AMERICAN

Industrial Hygiene

ASSOCIATION

Journal

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OCTOBER 1959

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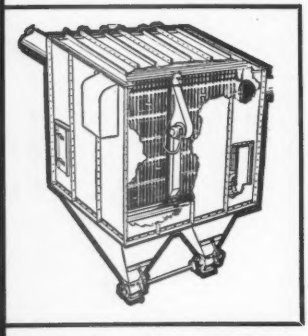
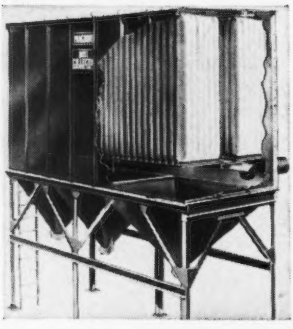


or automatic, *continuous* operation, the angborn Self-Cleaning Collector — ombining the proved efficiency of he cloth screen collector with con-inuous operation, uniform air flow.



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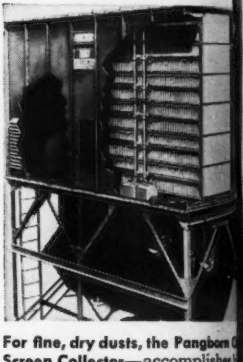

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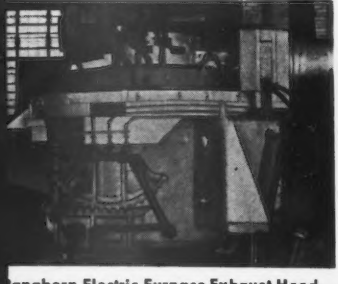

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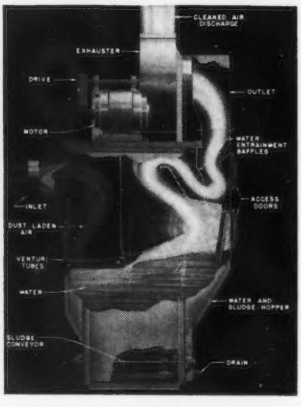

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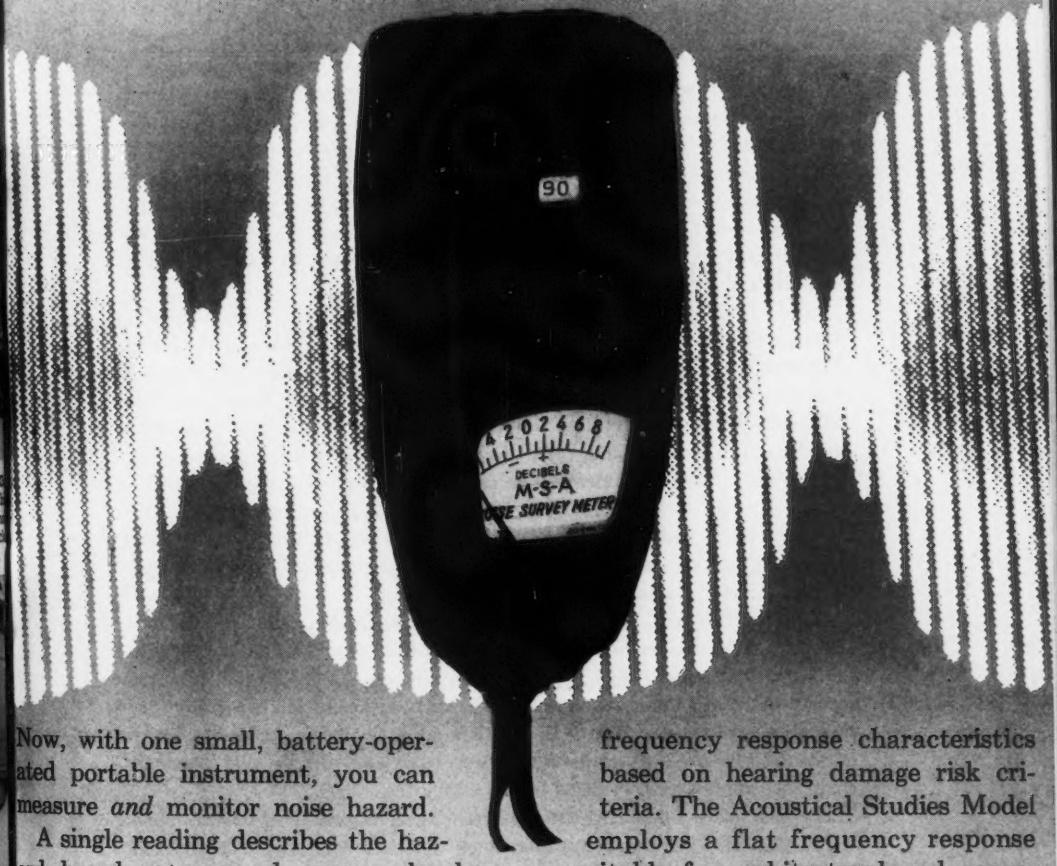

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President's Page

Industrial Hygiene is that science and art devoted to the recognition, evaluation and control of those environmental factors or stresses, arising in or from the work place, which may cause sickness, impaired health and well-being, or significant discomfort and inefficiency among workers or among the citizens of the community. Thus reads the new official definition approved by the Board of Directors of our Association. For many years there has existed a need for such a definition as well as a definition of an Industrial Hygienist and descriptions of the scope of Industrial Hygiene, the activities of an Industrial Hygienist and organization of the Industrial Hygiene activity.

Several committees have labored diligently in the past to develop suitable definitions and descriptions. Although their reports were accepted by the Board of Directors serving at the time each committee's report was received, adoption of recommended statements was withheld because eighteen Board members could not agree on exact wording for an official document in the time available to consider all committee reports at regular Board meetings. In the meantime, other professional associations, interested in one or more of the specialty fields of Industrial Hygiene, have published their definitions and statements representing their concepts of what we are, what we should be doing and where we should be established within an organization. Most of these concepts have been anathemas to a majority of our members.

In June of this year, an ad hoc committee was appointed, with Jack C. Radcliffe as Chairman, to review previous committee recommendations and to submit a final report which would resolve differences appearing in previous reports and which would take into consideration, comments and suggestions of present members of the Board. In addition, all of the past presidents were requested to review a draft copy—late in a series of many drafts—and to submit comments which were considered by the committee.

The result of the Committee's effort, appearing on page 428 of this issue, represents an unbelievable number of man-hours expended by many members, and most recently, by the five members of the ad hoc committee who eventually reached unanimous agreement on every word and point of punctuation. A covered reprint of this publication will be mailed to each member of the Association shortly.

Elmer P. Wheeler

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AMERICAN INDUSTRIAL HYGIENE ASSOCIATION JOURNAL, published bi-monthly for the American Industrial Hygiene Association. Dohrman H. Byers, *Editor;* Kenneth W. Nelson, *Associate Editor.* Editorial Offices, 1014 Broadway, Cincinnati 2, Ohio. Subscription $7.50 per year in the United States; $7.75 per year in Canada; $8.25 per year in all other foreign countries. Single copies $1.50. Entered as second class matter at the post office at Baltimore, Md. The American Industrial Hygiene Association Journal reserves the right to edit all advertisements and to refuse advertising copy when it does not meet the high standards adopted by the Association.

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The Toxicological Basis of Threshold Limit Values: 1. Experience with Threshold Limit Values Based on Animal Data*

HENRY F. SMYTH, Jr., Ph.D.

Mellon Institute, Pittsburgh, Pennsylvania and Union Carbide Corporation, New York, New York

IT IS clear that the ideal basis for defining the greatest concentration of a respirable substance which should be in the working environment is the prolonged critical examination of several considerable groups of workmen exposed to different constantly monitored concentrations. We do not have such a basis for controlling the working environment for any respirable substance. We are slowly approximating the ideal for the more widely used substances by the accretion of observations made during industrial operations. It is to be expected that most recorded observations will indicate undesirable conditions, and will tend to reduce the concentrations we consider satisfactory, so that the trend of changes in threshold limit values is downward.

It is obvious that the ideal cannot be attained before a new substance is put into use, because it can only be based upon results obtained after use begins. A variety of means have been employed in the past to predict safe working concentrations in advance of experience, with varying degrees of success. It is pertinent to inquire what means should be employed in the future, before a new respirable substance is to be put into use.

The best information we have on the greatest concentrations of respirable substances which are acceptable in the working environment is the accumulated experience of the profession of industrial hygiene, expressed in the annually revised list of threshold limits. One approach to determining what we should know before we set a new threshold limit in the future is the pragmatic course of examining the history of the individual threshold limit values.

In 1956 the author made a somewhat similar examination of the bases for threshold limits,[1] but at that time the emphasis was upon the total published evidence which tends to support or discredit each value, regardless of the date at which the evidence became available. The present inquiry is confined to the evidence which was stated to have been given most weight when each value was first proposed, or the evidence which is inferred on the basis of publication dates to have been ruling.

For the present purposes, any substance which has appeared in lists of threshold limits for at least five years is considered to have had sufficient observation in industrial use to be regarded as reasonably well understood, and its current threshold limit is considered to be sound. Accordingly, only substances for which threshold limits were first proposed in 1953 or earlier are considered. Furthermore the mineral dusts are completely excluded. The series of threshold limit lists considered begins with the U. S. Public Health service lists of 1943,[2] continues with the fully annotated 1945 list of Cook,[3] followed by the privately circulated and later published yearly lists of the American Conference of Governmental Industrial Hygienists starting in 1947,[4-10] with privately circulated annotations in 1953.[11]

The 1958 list of threshold limits[12] includes 148 substances which were first listed in 1953 or earlier. For the present purposes the 1958 threshold limits for these 148 substances are considered sound. For 87 of these substances the 1958 values are the same as those first proposed. That is to say, 59 per cent of the original threshold limit proposals remain unchanged after five or more years. It is a matter of individual taste whether this record is to be considered creditable or regrettable.

Examination of the data which were stated or are inferred to have been considered most important in selecting the initially proposed values for these 148 threshold limits, allows them to be divided into five classes, as is shown in Table I.

It would be grossly misleading to believe that this tabulation proves that analogy is the soundest basis for a threshold limit. Many analogies were relied upon in setting threshold limits because the substances were so little used that de-

* Presented at the Twentieth Annual Meeting of the American Industrial Hygiene Association, Chicago, Illinois, April 25–May 1, 1959.

tailed study was not worthwhile. Because most of these substances are still little used, experience has not accumulated to allow evaluation of the originally suggested limits, and the entry of 88 per cent in Table I is not a fair evaluation of the soundness of analogy.

It is gratifying to the toxicologist to see that limits originally based upon repeated inhalation studies with animals have stood up under several years scrutiny and experience as well as have those based upon industrial surveys. The only reason those based on brief human experiment have been almost 50 per cent successful, seems to be that most of these materials are limited in the industrial environment because of human sensory response, not because of true toxicity. It is not surprising that those based upon single inhalation by animals have not stood up well. Such a very limited toxicological study is likely to overlook objectional actions which will become obvious during continued human exposure.

Table II lists the 45 substances for which the first proposed threshold limit was based upon repeated inhalation by or feeding to animals, together wth references to the stated or inferred published data. The Table also gives the basis for later changes in each threshold limit, as well as the author can determine it. It should be pointed out that usually the threshold limit based on a toxicological study has not been suggested by the investigator himself, but is a value arrived at by a committee studying a report of the study.

Fifteen of these 45 threshold limits have been later changed, three of them changed twice. It should not be surprising that all but one of the changes are reductions. A single isolated observation of possible injury can result in reducing a threshold level, while it requires unusual opportunity, tenacity and motivation to collect the observations which would justify an increase in a threshold limit, as Sterner, Crouch, Brockmyre and Cusack did for butyl alcohol.[17]

The reasons for the 18 changes noted in Table II vary widely in apparent importance. They do not seem to yield any guidance toward making future studies more valid. Eight of the 18 changes were based upon observations made on humans. Five of these were undocumented statements of industrial experience, one was a severe injury, one was brief experimental human inhalation to judge organoleptic acceptability, and one consisted of ten years continuous observation of workmen in monitored environments. Ten of the 18 changes resulted from other considerations. Two were based on later more thorough and extensive animal experiment. Two were based on the principle that sound engineering control should prevent inhalation of any substance, other than carbon dioxide, at a concentration greater than 1000 ppm, no matter how innocuous it may be. Three were based on a more conservative reinterpretation of the original data, while three were substitutions of analogy for the original experimental data.

TABLE I

Stability of Threshold Limit Values First Proposed in 1953 or Earlier

Nature of original data	Substances first listed in 1953 or earlier	Substances with limits unchanged in 1958	Percentage of limits unchanged
Animals, repeated inhalation or feeding	45	30	67
Animals, single inhalation or injection	34	13	38
Human experience and surveys	26	17	65
Human experiment, brief	26	12	46
Analogy with better known substance	17	15	88
Total	148	87	59

It was hoped that a tabulation of the parameters of the 47 repeated inhalation studies would reveal short-comings in experimental design which had decreased the reliability of those threshold limits which were later changed. No consistent short-comings were revealed. There was a very wide range in the experimental designs. The studies ranged from four animals of one species to 91 of six species, inhaling vapor for 3 to 16 hours a day, for 17 to 384 days.

There was also a very wide range of conservatism displayed in the relation between the threshold limit proposed and the results of repeated inhalation by animals. If we define the safety factor as the greatest concentration which had no effect on animals, divided by the proposed threshold limit, the safety factors ranged from 0.2 to 10. For those threshold limits which were later changed, the median safety factor was 1.3, and for those which have not yet been changed it was 4. There was more conservatism manifested in suggesting those limits which have not been later changed.

The writer has earlier emphasized the fact that threshold limits are set because of a variety of objectionable effects. Following the lines of his 1956 article,[1] the most important injurious effects of the 45 threshold limits originally based upon repeated inhalation studies are summarized in Table III. It is clear that most of these threshold limits are not relied upon to guard against chronic toxic effects, although they were set on the basis of experiments designed to evaluate

TABLE II

History of Threshold Limit Values Based on Repeated Inhalation by Animals, and First Proposed in 1953 or Earlier

Substance	Threshold limit first proposed			Threshold limit changed			
	Year	ppm (or mg/m³)	Stated or inferred data	Year	ppm (or mg/m³)	Stated or inferred data	Basis
Acrylonitrile	1943	20	13				
Butadiene	1945	5000	14	1947	1000	—	Control
Butyl alcohol	1943	200	15	1945	50	16	Experience
				1950	100	17	Survey
Butyl CELLOSOLVE	1945	200	18, 19	1957	50	20	Rpt. animal
Carbon tetrachloride	1943	100	21	1947	50	22, p. 229	Experience
				1953	25	23	Rpt. animal
CELLOSOLVE	1945	200	18, 19				
CELLOSOLVE acetate	1945	100	24				
Chloroprene	1945	25	25				
Cyclohexane	1945	400	26				
Cyclohexanol	1945	100	26				
Cyclohexanone	1945	100	26				
Dichlorodifluoromethane	1945	100,000	27	1947	1000	—	Control
1,1-Dichloro-1-nitroethane	1945	10	28				
Diethyl amine	1952	25	29				
Dinitro-o-cresol	1949	0.2 mg.	30				
Ethyl amine	1952	25	29				
Ethylene dibromide	1953	25	31				
Ethyl silicate	1945	100	32				
Fluorine	1953	0.1	33				
Hydrogen chloride	1943	10	34	1948	5	22, p. 79	Experience
Isophorone	1945	25	35				
Mesityl oxide	1945	50	35	1958	25	—	Experience
Methyl alcohol	1943	200	36				
Methylal	1952	1000	37				
Methyl bromide	1945	20	38				
Methyl CELLOSOLVE	1945	100	18, 19	1947	25	39	Injuries
Methyl CELLOSOLVE acetate	1945	100	24	1947	25	—	Analogy
Methyl Chloroform	1953	500	40				
Methyl Cyclohexane	1945	1000	26	1947	500	—	Re-interpretation
Methyl cyclohexanol	1945	100	26				
Methyl cyclohexanone	1945	100	26				
Methylene chloride	1945	500	41				
Nitroethane	1945	200	42	1947	100	—	Re-interpretation
Nitromethane	1945	200	42	1947	100	—	Re-interpretation
Pentachloronaphthalene	1945	0.5 mg.	43				
Perchloroethylene	1943	200	44				
Phosphine	1943	1	45	1947	0.05	—	Analogy
Phosphorous, yellow	1947	0.1 mg.	46				
Propylene dichloride	1947	75	47				
Propyl ether, iso	1945	500	48				
Styrene monomer	1945	400	49	1947	200	50	Experience
				1957	100	22, p. 225	Analogy
Trichloronaphthalene	1945	5 mg.	43				
Turpentine	1943	200	15	1945	100	51	Human Experiment
Uranium, soluble	1953	0.05 mg.	52				
Uranium, insoluble	1953	0.25 mg.	53				

chronic toxicity. Nothing striking is revealed, although there has been some increased tendency to change in threshold limits which guard against irritation, and a decreased tendency to change in those guarding primarily against chronic toxicity. This simply confirms the obvious point that chronic toxicity can be judged better from animal experiment than can upper respiratory tract irritation.

There is a strong correlation between the year a threshold limit based upon repeated inhalation studies was first proposed, and the chances of its being later changed. Of eight proposed in 1943, five, or 63 per cent, have been changed. Of 26

TABLE III

Major Injurious Effect of Substances Whose Threshold Limit was Originally Based on Repeated Inhalation by Animals

Effect near threshold limit	30 threshold limits not yet changed		15 threshold limits later changed	
	Number	%	Number	%
Chronic toxicity	13	43	5	33
Acute effects	17	57	10	67
Acute toxicity	2	7	2	13
Narcosis	6	20	1	7
Narcosis and irritation	4	13	5	33
Lung injury	5	17	1	7
Asphyxia	0	0	1	7

proposed in 1945, ten, or 38 per cent, have been changed. Of 11 proposed in 1947 or later, none have been changed. Three factors seem to have contributed to this situation, the increased degree of health and comfort protection we now expect from a threshold limit, increasingly stringent standards for animal experimentation, and the length of time required to detect minor objections to a threshold limit by industrial experience.

Discussion

It is regrettable that this review of the toxicological stuides which have been used as the basis for threshold limit values does not reveal information by which the experimental design of future studies can be improved. It is beyond the scope of the present paper to make suggestions for improvement based upon experience in evaluating the safety of other uses of chemicals, such as food additives.

However, it is not out of place to point out that it is important in studying a new respirable substance to determine at the earliest possible moment what objectionable action occurs at low concentrations. If a threshold limit is required to guard workmen against slowly developing chronic toxic effects, quite prolonged and extensive animal experiment is called for. On the other hand, if a threshold limit must guard workmen only against eye, nose and throat irritation, or against reversible narcosis, animal experiment is less important than single human exposures to estimate the acceptability of low concentrations. If the substance is simply an inert asphyxiant, the threshold limit will be an arbitrary concentration representing good engineering control, far below an injurious level. If it is a sensitizer or carcinogen, the threshold limit will be practically zero. Once the nature of injury from very low concentrations has been definitely established elaboration of animal inhalation experiments is of value only in the case of the few substances which are chronically toxic.

Summary

The pragmatic test of experience shows that experimental study of the effects of repeated inhalation by animals has been as sound a basis for setting threshold limits as any other basis which has been applied to widely used respirable substances. Analysis of the details of the studies which underlie threshold limits gives no clear guide to the design of future toxicological studies, but it does emphasize the need for applying a safety factor when a threshold limit is based on toxicity studies.

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The Toxicological Basis of Threshold Limit Values: 2. Pathological and Biochemical Criteria*

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IN 1952, Smyth, Weil, Adams, and Hollingsworth published a paper entitled, *Efficiency of Criteria of Stress in Toxicological Tests.*[1] This paper summarized and discussed the collective experience of the Union Carbide Chemical Company Chemical Hygiene Fellowship at Mellon Institute and of the Biochemical Research Laboratory of The Dow Chemical Company with various tests commonly used in repeated dose toxicological studies. In essence, the study called attention to the high efficiency of liver and kidney weight studies as a measure of stress.

The data presented in Table I summarizes the information previously published, together with that obtained by the same two laboratories since the 1952 publication.

A summary of the frequency of particular observations is given in Tables II and III. They show that growth depression occurred frequently in both oral and inhalation studies and that it was a limiting criterion 11 per cent of the time. Hematological changes occurred occasionally but were limiting in only one study (benzene). Clinical changes in the urine were observed but twice in 43 instances where the urine was studied and neither time was the observation the only effect. Effect upon the functional ability of the central nervous system was observed with essentially the same frequency in inhalation studies as in oral studies and was the limiting factor each time it was observed. This was not unexpected because of the nature of the materials studied. Cholinesterase depression was the most sensitive criterion in a high percentage of the studies in which it was measured. Again, this was expected since cholinesterase levels were followed only in those studies involving materials known to cause such an effect because of preliminary observations or because of the chemical nature of the test material. It is recognized that cholinesterase depression might have been detected in some of the other studies included in this series had it been measured.

The frequency with which changes in the liver, kidney and lung occurred are summarized in Tables IV and V. It is worthy of note that with the liver and the kidney, the frequency of effect was high in both oral and inhalation studies. It is also interesting to note that although weight changes and pathological changes occurred with roughly similar regularity in the liver and kidney, weight changes in these two organs were more often the sole effect than were the morphological changes. The figures involving the lung are important because they show the importance of this organ when evaluating the effect of inhaling substances and its relative unimportance when evaluating the effect of ingestion. Certainly it would be expected that this would be the case but it is a bit surprising to find in this series of investigations that only once were lung changes limiting and this was a change in weight; not once was lung pathology the sole effect. It is undoubtedly true, however, that if the series had included such materials as silica, the results very likely would have been different.

A study of Table I shows that certain criteria were more frequently limiting than others. Hence, these are grouped in combinations as shown in Table VI for the purpose of showing which combinations were most informative. In this series, if observations had been limited to changes only in growth, liver weight and kidney weight, the dosage level causing an effect would have been detected about 80 per cent of the time. If only growth, liver pathology and kidney pathology had been studied, the dosage level causing an effect would have been determined but 59 per cent of the time. If only the five criteria, growth, liver and kidney weights, and liver and

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TABLE I

Summary of Observations at the Lowest Dosage Level at which Any Effect was Detected in Toxicity Studies Involving Repeated Administration over a Period of from One Month to Two Years

Criteria	Number of studies in which criterion was followed			Number in which a particular effect was found				Number in which particular effect was sole effect			
	Up to 1952	1952 1959	Total	Up to 1952	1952 1959	Total	%	Up to 1952	1952 1959	Total	%
Mortality	200	210	410	28	8	36	9	2	0	2	0.5
Food intake	138	173	311	25	3	28	9	1	0	1	0.3
Body weight	200	210	410	72	80	152	37	17	27	44	11
Organ weights											
Liver	154	210	364	89	85	174	48	28	26	54	15
Kidney	154	210	364	53	63	116	32	10	13	23	6.3
Heart	65	134	199	2	0	2	1	0	0	0	0
Spleen	67	134	201	7	6	13	6.5	0	0	0	0
Testes	54	132	186	4	4	8	4.2	0	0	0	0
Lung	45	134	179	1	6	7	3.9	0	1	1	0.6
Gross pathology	181	151	332	11	10	21	6.3	0	0	0	0
Micropathology											
Liver	190	190	380	65	71	136	36	10	5	15	4
Kidney	190	190	380	53	49	102	27	11	2	13	3.4
Heart	100	145	245	0	0	0	0	0	0	0	0
Spleen	133	154	287	6	1	7	2.4	0	0	0	0
Testes	117	152	269	1	8	9	3.3	0	1	1	0.4
Lung	80	167	247	6	8	14	5.7	0	0	0	0
Adrenal	136	150	286	1	1	2	0.7	0	0	0	0
Pancreas	102	139	241	0	0	0	0	0	0	0	0
Bone marrow	15	18	33	0	0	0	0	0	0	0	0
Voluntary muscle	27	5	32	0	0	0	0	0	0	0	0
Stomach	34	17	51	0	1	1	2	0	0	0	0
Intestine	83	19	102	3	0	3	3	0	0	0	0
Bladder	14	12	26	1	0	1	4	0	0	0	0
Neoplasms	10	19	29	0	0	0	0	0	0	0	0
Hematology	70	100	170	3	2	5	2.9	0	1	1	0.6
Blood urea nitrogen	64	53	117	5	0	5	4.3	0	0	0	0
Clinical urine analyses	29	14	43	1	1	2	4.6	0	0	0	0
Central nervous system		141	141		5	5	3.5		5	5	3.5
Cholinesterase		10	10		8	8	80		4	4	40

TABLE II

Frequency with which a Particular Effect was Observed at the Lowest Dosage Level at which Any Effect was Observed

Criteria of effect	Data from 1952–1959				Data from last 22–25 years	
	Oral		Vapor		All routes	
	*	%	*	%	*	%
Growth	64 (172)	37	16 (38)	42	152 (410)	37
Hematology	1 (79)	1.3	1 (21)	5	5 (170)	2.9
Clinical urines	1 (7)	14	0 (7)	0	2 (43)	4.6
CNS	4 (109)	3.7	1 (32)	3.1	5 (141)	3.5
Cholinesterase	8 (10)	80	—	—	8 (10)	80

* Number of positive findings (number of observations)

TABLE III

Frequency with which a Particular Effect was the Sole Effect at the Lowest Dosage Level at which Any Effect was Observed

Criteria of effect	Data from 1952–1959				Data from last 22–25 years	
	Oral		Vapor		All routes	
	*	%	*	%	*	%
Growth	25 (172)	15	2 (38)	5	44 (410)	11
Hematology	0 (79)	0	1 (21)	5	1 (170)	0.6
Clinical urine	0 (7)	0	0 (7)	0	0 (43)	0
CNS	4 (109)	3.7	1 (32)	3.1	5 (141)	3.5
Cholinesterase	4 (10)	40	—	—	4 (10)	40

* Number of positive findings (number of observations)

TABLE IV

Frequency with which a Particular Effect was Observed at the Lowest Dosage Level at which Any Effect was Observed

Criteria of effect	Data from 1952–1959				Data from last 22–25 years	
	Oral		Vapor		All routes	
	*	%	*	%	*	%
Liver						
Weight.....	70 (172)	41	15 (38)	40	174 (364)	48
Pathology..	50 (172)	29	21 (38)	55	136 (380)	36
Kidney						
Weight.....	50 (152)	33	13 (38)	34	116 (364)	32
Pathology..	33 (152)	22	16 (38)	42	102 (364)	27
Lung						
Weight.....	1 (102)	1	5 (32)	16	7 (179)	3.9
Pathology..	0 (131)	0	8 (36)	22	14 (247)	5.7

* Number of positive findings (number of observations)

TABLE V

Frequency with which a Particular Effect was the Sole Effect at the Lowest Dosage Level at which Any Effect was Observed

Criteria of effect	Data from 1952–1959				Data from last 22–25 years	
	Oral		Vapor		All routes	
	*	%	*	%	*	%
Liver						
Weight.....	25 (172)	15	1 (38)	2.6	54 (364)	15
Pathology..	5 (152)	3.3	0 (38)	0	15 (380)	4
Kidney						
Weight.....	13 (172)	7.6	0 (38)	0	23 (364)	6.3
Pathology..	2 (152)	1.3	0 (38)	0	13 (380)	3.4
Lung						
Weight.....	0 (102)	0	1 (32)	3	1 (179)	0.6
Pathology..	0 (131)	0	0 (36)	0	0 (247)	0

* Number of positive findings (number of observations)

kidney histopathology had been studied, the lowest dosage level found to cause any effect would have been detected in 96 per cent of the cases. It is readily apparent, therefore, that these five criteria as a group were far more efficient in detecting first signs of adverse effect than most of the numerous other studies quite commonly included in toxicological investigations.

Those criteria which make up the balance of 4 per cent of the limiting observations in this series of studies deserve some comment, for they can be extremely important. Excessive mortality was observed twice. Food intake, an increase in lung weight, testicular injury, and hematological changes were observed once each. CNS depression was observed to be limiting five times. Cholinesterase depression was found to be limiting four times. Effect on mortality, food intake and CNS depression are always observed in any well conducted toxicological study of significance and are readily available for a minimum of effort. Measurement of cholinesterase levels in the blood is now routine when studying any material suspected of having such activity. A decision whether such activity should be followed in a long term study can be gained by observation of the signs displayed by animals treated with large doses either singly or repeatedly, by direct measurement of the cholinesterase content of the blood of such treated animals, or by associating the chemical structure of the test material with other chemicals known to be cholinesterase inhibitors.

TABLE VI

Per Cent of Studies in which One or More Effects of a Combination were Observed at the Lowest Dosage Level at which Any Effect was Found

Criteria of effect (Combinations)	No. of studies involved	Oral	Vapor	All studies
Growth Liver weights Kidney weights	364	82	73	80
Growth Liver pathology Kidney pathology	380	56	75	59
Growth Liver weights Liver pathology Kidney weights Kidney pathology	364	97	88	96

In the past, our laboratories have engaged in many time-consuming and expensive studies of certain criteria which have yielded a very poor return in terms of positive findings. These are shown in Table I. Most important of this group are neoplasms. Although no neoplasms attributable to the experimental routine occurred at the lowest dosage level at which any effect was found in any of the 29 one to two-year studies included in this series, observations for such occurrences are of prime importance. In fact, the basic reason for conducting lifetime studies on the rat is to determine whether the material in question has the capacity to induce neoplasia. The occurrence of neoplasms at any dosage is cause for careful thought when threshold limit values are being established.

In this day and age, there is much pressure upon all toxicologists to do more and more in an effort to find the threshold limit beyond

reasonable doubt. This is an admirable objective, one toward which all toxicologists strive. On the other hand, it is necessary to be realistic and practical and to make the most of the limited time and money which is available for such investigations. There always has been and always will be more that could be done on any project; the question is, "Is it worth the effort?" Many persons have spent their lifetime studying the physiological properties of a single material or perhaps a limited series of closely related materials. The value of such endeavors can not be disputed for much good has come from them.

Unfortunately, there is not enough manpower, time, or money to allow such exhaustive studies to be made upon the thousands of chemicals or compositions facing the public today, nor is it generally necessary or desirable that such be done. From the standpoint of the worker and the public, it is far more desirable to expend a generous portion of the resources available in determining the basic physiological properties of many chemicals rather than exhaustively studying a very few. By so doing, it is possible to eliminate or control many of the hazards to health which otherwise would be discovered only by unfortunate experience. It must be pointed out, however, that there are problems of a toxicological nature which can only be answered by exhaustive research. When the need for such study is justified, there is no choice but to proceed.

The criteria considered in Table I are old and quite well accepted. New criteria, new methods and new instruments are continuously being researched and developed. Many of these new criteria are in limited use today but sufficient data are not yet available to properly assess their value in relation to the time tested criteria.

For example, new tests are being developed to measure the capacity of certain vital organs to perform their duty. It is hoped, and there is reason to believe, that they will prove to be more efficient than the tests commonly employed at present. New techniques are being developed to allow the study of materials on individual tissues and cells, and even upon the intracellular bodies and fluids. It is hoped that these will shed light upon mechanism of action. New machines are now available which can rapidly and almost automatically do clinical blood and urine analyses and even cholinesterase determinations. Research will undoubtedly adapt them to other chemical and physical procedures which today require many hours of hand labor. Hence, the capacity for more and better investigations is being increased. Metabolism studies always have been and always will be basic to an understanding of the physiological properties of chemicals. In the past, methods for the most part have been laborious and time consuming. Progress is being made and in the future, instrumentation will make the metabolism study easier, better, and more practical. The development of more economical, more sensitive, and more foolproof instruments such as the mass spectrograph, vapor phase chomatograph, ultraviolet, infrared, and emission spectrograph, and better instruments for radiochemical studies are now providing welcome assists to the biochemist. In fact, the enormous potentialities of such instruments in the biochemical aspects of physiology, pharmacology, and toxicology are only beginning to be appreciated.

In spite of the fact that there are many new criteria being developed and tested today, the data presented herein emphasize the high value of certain of the older criteria. It would seem only prudent to make use of those studies which experience has shown to be most productive. This does **not** mean that **only** those criteria showing a high degree of efficiency in the series of investigations reported herein should be used, but certainly it suggests that they should be basic to any toxicological study designed to determine a threshold limit for repeated exposure.

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Scientific Exhibits for Industrial Health Conference

EACH YEAR THE SCIENTIFIC EXHIBITS are an important and greatly appreciated part of the Industrial Health Conference. Applications are now being accepted for space for Scientific Exhibits desired to be shown at the 1960 Industrial Health Conference. Exhibits will be shown from April 26 through April 28. Forms and information may be obtained from George A. Hardie, Chairman of Scientific Exhibits Committee, 343 State Street, Rochester 4, New York.

The Toxicological Basis of Threshold Limit Values: 3. Physiological Criteria

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IN THE first paper of this Symposium, H. F. Smyth, Jr.[1] has pointed out that presently accepted Threshold Limit Values have been based on a variety of criteria. Some of them seem in retrospect to have been established on very meager evidence indeed. Some are well grounded on animal experimentation and human experience. A number have been based on physiological criteria, among them the Threshold Limit Values for those substances which, like ethyl alcohol, ethyl ether, and gasoline, impair judgement and delay reaction time at exposure levels below those causing any recognizable organic lesion. Indeed Smyth in his 1956 Cummings Memorial Lecture[2] recommended that the Threshold Limit Value for a narcotic substance should be a concentration which produces no detectable effect on judgement and reaction time after eight hours' inhalation. This would seem to be a very reasonable specification.

It is worth considering, however, whether physiological criteria might not have a broader usefulness in connection with the establishment of Threshold Limit Values than the one just mentioned. I will suggest that they have value also for compounds whose effects are not primarily narcotic or obviously productive of functional disturbances.

In a paper published in 1947[3] I tried to characterize the states of health observed among workers (or the general population for that matter) as follows: (a) the state of good health in which the individual is able to work and live effectively and without undue strain on his inner resources; (b) an intermediate state in which he is able to work and live but only under a feeling of tension, strain or discomfort; and (c) poor health, in which excessive changes in the physical, chemical, or functional components of the organism cause a definite impairment in the ability of the individual to lead a normal existence.

The state of poor health as defined above was once considered to be the inevitable accompaniment of industrial employment. Thackrah,[4] writing in 1831, noted that miners seldom attained the age of 40, that fork grinders die at the age of 28 or 32, and that table knife grinders on the other hand survive to between 40 and 50. He further stated: "Most persons who reflect on the subject, will be inclined to admit that our employments are in a considerable degree injurious to health; but they believe, or profess to believe, that the evils can produce only pain and discontent." He added: "Evils are suffered to exist, even when the means of correction are known and easily applied."

Today, conditions of employment which are frankly injurious to health are not tolerated but perhaps we are still not fully aware of those evils which produce "only pain and discontent." Selye, to cite his recent popular work *The Stress of Life*,[5] makes much of the adaptation to the stresses and strains of everyday life, but does not mention the possibility that among these might be considered occupational exposure to chemicals at levels below those causing definite occupational disease. If such exist and are to be recognized, physiological or functional criteria must be applied.

The industrial toxicologist recognizes that chemicals cannot simply be classified into those which are poisonous and deleterious and those which are not poisonous and deleterious. Toxicity is a function of the amount of the chemical entering the body, and even so-called safe materials like sodium chloride, baking soda or water can produce serious bodily injury if the dose is large enough. His task is to develop information which makes possible the use of chemicals in industry—and in the home—without the necessity for even minimal bodily injury.

But what is minimal bodily injury? It is certainly something far short of death. It is less than a condition of poor health. It lies in the area of intermediate health, referred to above, where one works and lives but only under a feeling of tension, strain or discomfort. I would certainly include under minimal bodily injury

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those states in which judgement is impaired or reaction time delayed, even though no anatomical lesion may be demonstrable with present investigative techniques. We may leave open the question as to whether or not anatomical or biochemical lesions might be demonstrable if sufficiently sensitive techniques were available. It suffices to say that a decrement in physiological function may be the only injury apparent to the observer. In this sense, industrial toxicology should be very much concerned with physiology, and directly concerned in the establishment of Threshold Limit Values.

There is good precedent for the toxicologist to be interested in physiology. Claude Bernard in his *Introduction to the Study of Experimental Medicine*[6] wrote in 1865 of the complex living organism: "Here is an organic or social interdependence which sustains a sort of perpetual motion, until some disorder or stoppage of a necessary vital unit upsets the equilibrium, or leads to disturbance or stoppage in the play of the animal machine." He continues: "By examples cited further on we shall see how a dislocation of the organism or an apparently highly complex disorder may be traced back to an initial simple determinism which later produces more complex determinisms. A case in point is poisoning by carbon monoxide. I am devoting my whole course at the College de France this year to the study of curare, not for the sake of the substance itself, but because this study shows us how the simplest single determinism, such as the lesion of a terminal motor nerve, re-echoing successively from all the other vital units, leads to secondary determinisms which grow more and more complicated until death ensues." (p. 88.)

Bernard here is working back from complex observed phenomena to the relatively simple originating disturbances which by "re-echoing necessarily from all the other vital units" produce the complex phenomena. We may find that by paying attention to these echoes we can detect minimal toxic effects more readily than by observing the primary disturbance which may, at an early stage, be unrecognizable by our investigative techniques.

Observations reported by Foulger[7] in 1943 on the response of the blood pressure of workers to exposure to chemicals led the Haskell Laboratory to investigate the possibility that blood pressure changes in the dog might provide an early indication of effects from exposure to chemicals. Some of the results of the application of this technique were reported to the American Industrial Hygiene Association at the April 24, 1952 Meeting.[8]

In brief, the systolic and diastolic blood pressures were determined by the indirect method using a pediatric cuff, mercury manometer, and combination of stethoscope pick-up, amplifier and wall-mounted speaker for detection of the sounds. The technique is illustrated in Figure 1. It can be seen that the measurements are made with the dog standing quietly and without restraint. The two-strap type of cuff is most suitable for dog work because it can be adjusted to the taper of the dog's leg and will not slip if properly applied. Blood pressures were measured twice daily, five days a week and, after a brief training period, the measurements were accepted by the dogs as a part of their routine and provoked no emotional response. This technique is still used in the Haskell Laboratory.

FIGURE 1. Method for taking blood pressure of dogs. Sound-proof rooms are used for taking data on dogs' oxygen consumption, blood pressure, and pulse.

Figure 2 shows the blood pressure record of a control dog observed over a period of 14 months. Each dot represents the average of four consecutive measurements and the parallel lines are placed at plus and minus three standard errors of the mean of the groups of four measurements. It was concluded that there were no consistent seasonal trends but that a slight variation could be traced to the use of two different observers. These charts, which are plotted like conventional quality control charts, provide a framework in which statistically significant deviations from normal can be detected.

Figure 3 shows the blood pressure record of a dog exposed to chlorotrifluoroethylene, (CTFE), and is taken from the paper presented in 1956[9] before the American Industrial Hygiene Association by Hood, et al. of the Haskell Laboratory. No changes in blood pressure were observed at 15 and 30 ppm. At 50 ppm, however, an upward trend in systolic, diastolic and pulse pressure is observable. At 100 ppm the changes became statistically significant.

Hematological changes also began to appear during the 50 ppm exposures. These are shown

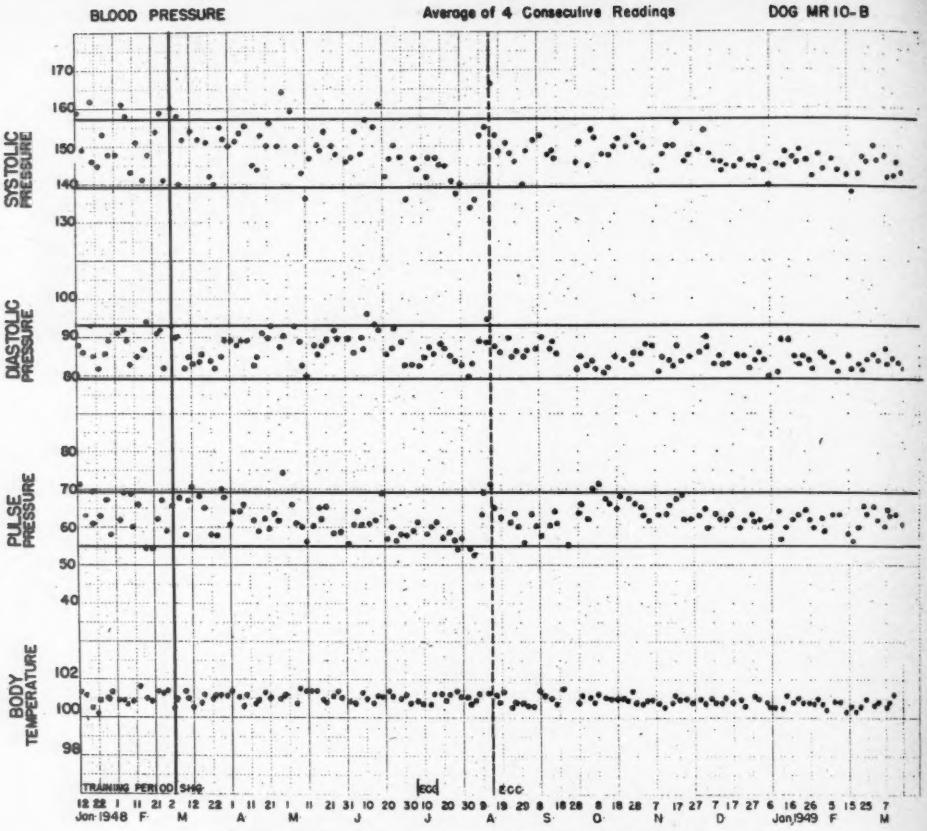

FIGURE 2. Blood pressure control chart of normal dog.

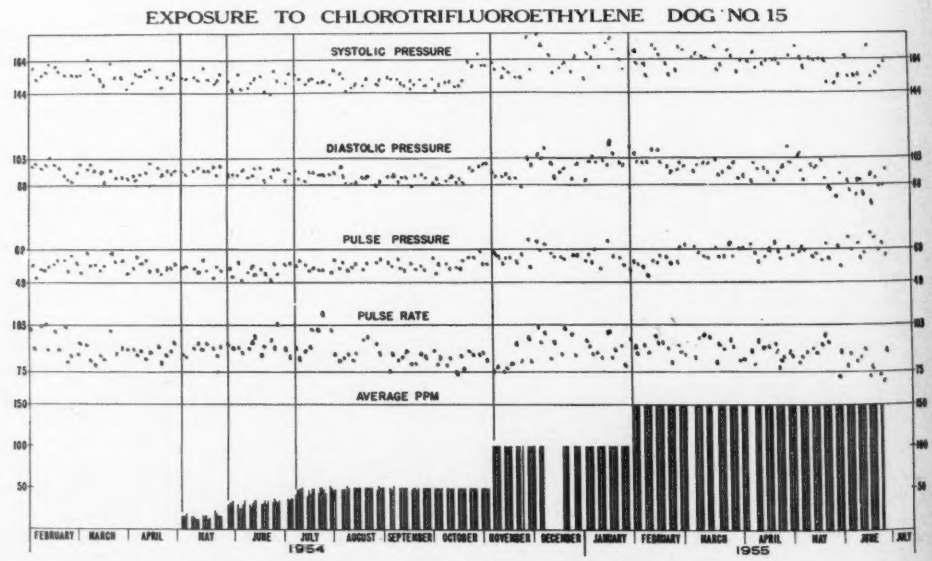

FIGURE 3. Blood pressure control chart of dog exposed to chlorotrifluoroethylene.

TABLE I

Hematological Summary of Dogs Exposed to Chlorotrifluoroethylene (CTFE)

Dog No.	PPM	RBC × 10^6/mm³	Hb gm/100 ml	Ht %	Cell Size μ	WBC/mm³	Differential						
							Neut	Lymph	Eosin	Mono	Baso	Atp Neut	Nucleated RBC/100 Cells
16	0	7.15	16.9	51	7.0	11830	53	30	15	0.5	0.4	1.0	0.3
		±0.38	±1.1	±0.9	±0.4	±2730	±10	±11	±0.5				
	15	7.00	16.7	50	6.9	9050	50	27	20	0	3	0.5	1.0
	30	7.21	17.3	51	7.0	10530	47	34	16	0.3	1	1.0	1.0
	50	7.50	17.4	52	7.0	10930	43	33	21	0.5	0.7	1.4	1.0
	100	7.24	16.8	50	7.0	8460	43	37	16	2	0	1.0	0.4
	150	7.72	17.6	54	7.0	6165	44	37	14	4	0	0	0.6
	0	7.01	16.2	49	7.1	9590	53	27	14	4	1	0	0
18	0	6.85	16.4	50	6.8	13040	65	21	10	3	0	1	0.4
		±0.42	±0.9	±2.0	±0.5	±4390	±7	±6	±4				
	100	7.69	18.4	53	6.8	7420	56	35	7	2	0	1	0
	150	7.68	18.2	55	6.8	5010	53	39	6	1.3	0	0	0
23	0	5.88	14.1	41	7.1	15730	54	13	29	1	0	2	0.5
		0.39	±0.6	±1.7	±0.5	±4130	±16	±6	±13				
	100	6.97	16.3	48	6.9	6970	34	45	18	2	0	1	0
	150	7.29	17.3	51	6.7	5310	35	44	16	3	0	1	0

in Table I. The changes became statistically significant at 100 ppm. Clinical signs of toxicity were not observed during exposures to 15, 30, 50 or 100 ppm of CTFE. After 56 exposures to 100 ppm the concentration was raised to 150 ppm. After 27 and 64 exposures respectively to 150 ppm of CTFE, two dogs showed definite signs of clinical neurological disturbance. A third dog died suddenly after the 54th exposure to 150 ppm.

Thus in this experiment changes in blood pressure, as well as hematological changes, occurred at an exposure level unproductive of any clinical signs of toxicity.

Chlorotrifluoroethylene is a chemical which produces different effects in rats than in dogs. Chronic exposure of rats to concentrations of CTFE ranging from 15 to 150 ppm over 14 months was carried out simultaneously with exposure of the dogs and in the same exposure chamber. The rats showed no clinical signs of toxicity, but severe renal tubular necrosis was found on sacrifice. One interesting observation had been made, however, and that was that the rats exposed to CTFE excreted larger volumes of urine than the control rats.

It happened that at this time in our Laboratory, Dr. E. P. Radford, Jr. was developing quantitative tests of renal function suitable for use in chronic toxicity experiments. The kidney function test that showed most promise was that which measured the ability of the kidneys to produce a concentrated urine. Rats were found to be particularly useful for studies of the renal concentrating function because even when given free access to water they restrict their intake voluntarily and excrete an almost maximally concentrated urine. Furthermore, the normal renal concentrating ability of rats is rather uniform and the normal range of urine concentration is narrow, so that deviations can be readily detected.

Radford set up a special experiment with CTFE in which four groups of six rats each were exposed once to CTFE for four hours. The concentrations used were 125, 240, 340 and 460 ppm respectively. At the highest dose three of the six rats died, the deaths occurring on the third, fourth and fifth days after exposure. All survived the lower exposures. Figure 4 shows the effect of these exposures on urine concentration. Using the rats as their own controls it can be seen that even a single exposure caused a graded response in terms of urine concentration. Figure 5 compares CTFE with $HgCl_2$ administered subcutaneously. Both of these figures are taken from a forthcoming paper by Dr. Radford on nephrotoxins.

It is obvious that a study of urine concentration during our chronic CTFE exposures might have been quite rewarding. We are applying the test in chronic toxicity studies with a fluorocar-

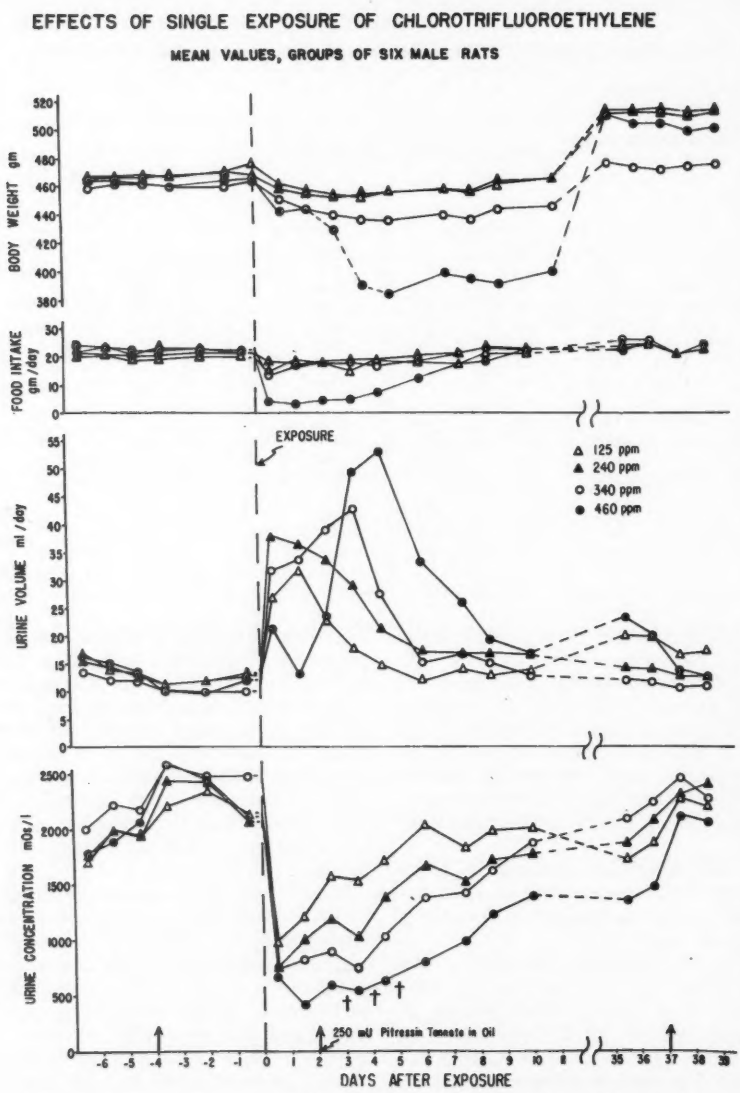

FIGURE 4. Renal function as influenced by exposure to chlorotrifluoroethylene.

bon gas currently under investigation in our laboratory, and the indications are that it will be helpful in enabling us to arrive at an estimate of the Threshold Limit Value.

Selye in the reference cited[8] points to the kidney and arterial blood pressure regulation as frequently responsive to stress. Studies of arterial blood pressure and renal function may, therefore, be worth considering in chronic toxicity experiments even though the effects may be echoes rather than the primary determinisms of Bernard's terminology. Other physiological criteria which have been used with some success in our Laboratory include observations of spontaneous activity of small animals in activity cages, ability of animals to maintain their balance on a slowly revolving roller, work performance of dogs on a treadmill, and modification of reflex responses.

In 1957 Dr. C. R. Williams brought back from

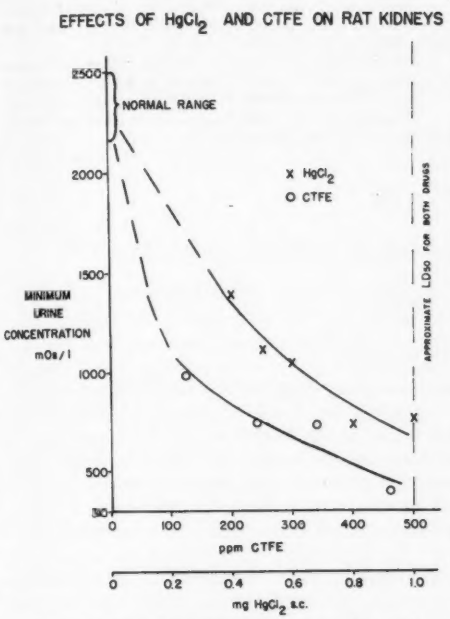

FIGURE 5. Renal function as influenced by chlorotrifluoroethylene and mercury chloride.

Helsinki a copy of a paper by Z. V. Smelyansky of the U.S.S.R. entitled *Establishment of Standard Hygienic Orders with Reference to Maximum Allowable Concentrations of Toxic Substances in the Air of Workrooms.*[10] Copies of a translation of this paper were subsequently made available to members of the American Industrial Hygiene Association. It is apparent from this paper that Russian toxicologists have not neglected physiological criteria in establishing Threshold Limit Values. Table II shows Threshold Limit Values determined for five compounds on the basis of morphological, clinical and physiological criteria. Smelyansky comments: "As shown in the table, physiological investigative methods have proven to be important sensitive tests in comparison with other methods, including morphological studies."

TABLE II

Russian Threshold Limit Values Based on Different Criteria

	Morphological changes	Clinical symptoms	Change of the muscle output capability	Change of the conditoned reflex action
	Minimum concentration mg/l			
Ethyl acetate	7.0	3.5	1.5	0.5
Dioxane	7.5	5.0	—	0.5
Nitropropane	5.8	—	0.2	0.1
Tetranitromethane	0.1	0.1	0.003	0.003
Diethylamine	3.0	2.0	2.9	0.25

From Z. V. Smelyansky[10]

The Russian investigators have apparently made considerable use of the Pavlov conditioned reflex as an investigative tool in the detection of effects from chemical exposure. In Smelyansky's words: "The Pavlov method has made it possible to detect the action on the organism of minimum concentrations of many toxic materials which would not be possible by the use of other investigative methods; the central nervous system of human beings and animals is very sensitive to all kinds of environmental changes."

A word of caution about the use of physiological criteria in determining Threshold Limit Values is indicated. Not all physiological changes are presumptively harmful. Some may merely represent the organisms normal and completely adequate response to an environmental change. Here, as always, the good judgement of the investigator is essential. In my opinion, however, physiological criteria should never be neglected for they show promise of giving better and often quicker answers to the troublesome question of what is a safe exposure.

There is an additional thought on which I should like to close. No Threshold Limit Value should be accepted without reservation as to its applicability to human beings. Tentative values should be reappraised in the light of human experience. It is in this area particularly that the application of non-destructive physiological tests to exposed workmen may reveal whether or not a tentative Threshold Limit Value is indeed one under which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

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AIHA CUMULATIVE INDEX

A CUMULATIVE INDEX of the American Industrial Hygiene Association Quarterly from 1940 through 1957 (Volumes 1 through 18) has been completed. This Index was compiled in conjunction with the offering of complete sets of bound volumes of the Quarterly and provides a valuable key to a great deal of important information on industrial hygiene published over these eighteen years. Because of its value as a reference source, the Cumulative Index is being made available for purchase as a separate item. The Index is available in either soft or hard cover until further notice. The price schedule is:

Members:	soft cover $10.00	Non-members:	soft cover $15.00
	hard cover 15.00		hard cover 20.00

Orders and inquiries should be directed to Executive Secretary, American Industrial Hygiene Association, 14125 Prevost, Detroit 27, Michigan.

THIRTEENTH INTERNATIONAL CONGRESS ON OCCUPATIONAL HEALTH

THE THIRTEENTH INTERNATIONAL CONGRESS on Occupational Health will meet at the Waldorf-Astoria Hotel, New York City, July 25–29, 1960. The Congress on Occupational Health is held every three years under the auspices of the Permanent Committee and International Association on Occupational Health. The five-day program will present both specific and general papers and discussions in many areas such as: medical practices, social and legal aspects, environmental hygiene, administrative problems, training, physiology and psychology in work situations, and others. Exhibits, social events, field trips, and post convention tours are planned.

There is still opportunity to offer papers for this program. Persons desiring to present papers should write as soon as possible to Dr. Irving R. Tabershaw, 375 Park Avenue, New York, New York, U.S.A.

Inquiries concerning attendance, registration, hotel accommodations, and other matters should be directed to Dr. R. E. Eckardt, P.O. Box 45, Linden, New Jersey, U.S.A. Registration and reservations should be made by May 1, 1960.

The Toxicological Basis of Threshold Limit Values: 4. Theoretical Approach to Prediction of Toxicity of Mixtures*

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THE DETERMINATION of toxicities must precede the establishment of threshold limit values even for single substances. While the large amount of animal experimentation and human experience recorded in the literature has allowed us to determine the relative toxicities of many individual substances and even of a few mixtures, other chemicals remain unstudied and new ones are appearing every day. As a consequence, many are still unevaluated. If the assessment of the toxicity of individual compounds lags it is evident that only an insignificant fraction of all their possible mixtures can be examined experimentally. Because the toxicities of their ingredients are not always additive it is unsafe to calculate for mixtures. The alternative is to develop theoretical approaches to the prediction of the toxicity of mixtures. Some progress has been made in this direction.

In two important papers Brieger[1, 2] has reported his literature surveys for examples of synergistic and antagonistic physiological effects of exposure to multiple air contaminants. Even he, however, has made only a limited approach to the prediction of the toxicity of mixtures. In a paper which preceded Brieger's second one Ball[3] reviewed work in the pesticide field which, employing Finney's modification of Bliss' mathematical treatment, offered promise in the prediction of the toxicity of mixtures.

Although we eventually encounter situations in which our knowledge is insufficient to permit us to make reliable predictions, progress can be made by working from known ground. It is logical to first look for the chemical and physical reactions which may take place in a mixture, before it even reaches the test organism.

Effect of Chemical Reactions on the Toxicity of Mixtures

Because they are less complex, chemical reactions are better understood than are physical ones and more is known about the latter than about physiological action.

A knowledge of chemistry is a prerequisite to the prediction of the toxicity of mixtures because the compounds which reach the test organism may have very different properties than the ingredients brought together in the mixture. Perhaps the simplest example is that of a strong acid such as hydrochloric reacting with a strong base, say sodium hydroxide. The products are water and common salt. On the other hand, to form the salts of some organic compounds is to make them more soluble and thus more toxic.

Possibly the most important finding in the Los Angeles air pollution studies[4] was that irritating organic oxidation products and peroxides arise from the chemical reaction of atmospheric ozone and nitrogen oxides with the unsaturated hydrocarbons from internal combustion engines. Another example of chemical reaction is in Adams and Schneider's report[5] that styrene and halogens react in the atmosphere to yield eye irritants.

Even the isomers of physiologically active compounds may vary in their effect. Years ago[6] it was found that 1-atropine was twice as active as the d-1 mixture and twenty times as active as d-atropine. It was well known[7] that the gamma isomer of benzene hexachloride is the only one which is an effective insecticide.

These divergent examples illustrate the value of a knowledge of chemistry as an aid to predicting the physiological activity of mixtures.

Effect of Physical Reaction on the Toxicity of Mixtures

Perhaps because chemical reaction products can be predicted or determined analytically in many cases, toxicologists have directed more attention to physical interactions. Among the effects which have been studied are those due to change in size, shape and density of particles, the action of electric charges on the aggregation of aerosols, the action of particulates in collecting and transporting liquids and gases and of

* Presented at the Twentieth Annual Meeting of the American Industrial Hygiene Association, Chicago, Illinois, April 25-May 1, 1959.

aerosols on the physiological action of particulates, liquids and gases.

La Belle and co-workers[8] in a significant paper on the synergistic effects of aerosols review the work of Schrenk, Vorwold, Magill and Dautrebande on the role of aerosols on the action of irritating and toxic compounds. The latter two investigators reported that the presence of large particles of sodium chloride, mineral oil and silica increased the eye irritation caused by formaldehyde and nitric acid fumes. The presence of small particles, on the other hand, increased lung deposition. La Belle et al. exposed mice to each of the following as disperse phase: triethylene glycol, ethylene glycol, mineral oil, glycerin, sodium chloride, the filter aids Dicalite and Celite, Attapulgus clay and Santocel CF (a silica gel). By statistical analysis of the ratio of lung weight to body weight they showed that the aerosols themselves had no significant effect on mice. They then exposed mice to formaldehyde, acrolein and nitric acid in the presence of each of these compounds and recorded survival times. In summarizing their results they found that when aerosols are added to atmospheres containing formaldehyde vapor, the typical effect is to increase the toxicity. Aerosols added to nitric acid fumes tend to decrease the toxicity, while the addition of aerosols to acrolein vapor has variable or no effect on toxicity.

They point out that the penetration of gases through the nose ranges from a fraction of 1% for a gas like hydrochloric acid to 100% for nitrogen. The penetration of aerosols ranges from about 20% for 5μ particles to 100% for 1μ particles.

La Belle and co-workers state that the effects of aerosols in altering the toxicity of irritant gases is closely and directly related to the relative penetration of particles and vapor molecules present. When vapor penetration exceeds particle penetration, toxicity is decreased. If aerosol penetration exceeds vapor penetration, toxicity is increased. There must, however, be physical combination between vapor and aerosol (absorption, adsorption, solution) or no change in the toxicity of the former will occur. The theory explains the findings of Daubrebande and others, who conclude that external increases were caused by large particles and that lung symptoms were due to the smaller ones, for it is reasonable to expect that the large particles (10μ) mentioned by these authors would have lower penetration than formaldehyde and nitric oxide and therefore would be predicted to increase the quantity of vapor reaching the nasal linings.

They give a table of the calculated penetration of 21 gases through the nasal passages based on: (1) Henry's law, (2) the ratio of mols of gas to mols of liquid in the system, (3) the estimated number of transfer units in the upper respiratory passages and point out that a similar tabulation can be made of the probable penetration of particles through the nasal passages.

With this data it is possible to predict the probable effect of a given aerosol on the toxicity of a vapor. If this excellent work could be paralleled in other cases we would have made great strides toward the theoretical prediction of the toxicity due to physical interaction.

Sumerford[9] has reviewed physical synergism in the case of insecticides and drawn certain conclusions. Agents which increase coverage of foliage, decrease evaporation, prevent crystallization, provide adhesiveness, aid in distribution or suspension, and increase penetration of insect cuticle tend to increase the toxicity of insecticides for insects. Appropriate chemicals which release insecticide in active form (nicotine from the alkaloid), stabilize (effect of pyrethrine on DDT or parathion) or bring them to optimum pH (nitrocresol) increase their effectiveness.

Effect of Joint Action in Vivo on the Toxicity of Mixtures

When we progress from the study of chemical and physical reactions in mixtures outside the body to the examination of the joint action of materials in vivo we find ourselves on more uncertain ground. The literature reports of synergistic or antagonistic physiological effects of exposure to multiple air contaminants are becoming more numerous. In the second of his aforementioned papers Brieger[2] has catalogued much of this work and made significant observations.

He points out that two or more gases or vapors that have the same biological target may inflict greater injury than the sum of their individual effects. This is true even if their mechanisms of action differ. Brieger cites work he did with La Belle on a mixture of solvents with identical sites and mechanism of action but different degrees of toxicity. The effect of exposure of animals to the mixture did not differ from exposure to an equal amount of the main component. He reports a synergistic effect, described in the literature, from toluene and butyl acetate administered together and mentions the marked potentiation in mammalion toxicity found by Frawley and co-workers from the simultaneous administration of two anticholinesterase compounds. He also cites the work of Stokinger et al., von Oettingen, Hough et al., McCollister et al., Smith and Mayers, and Quadland. All

these references are to synergism or possible synergism. There are also reports of synergism in the literature by Drinker and co-workers,[10] Amdur,[11] Russians[12] and others.

On the other hand, as Brieger states, there is little evidence of physiologic antagonism of multiple air contaminating agents in the same physical state. He quotes, with reservation, Mittler, Hedrick and Phillips who found a decrease in the toxicity of ozone administered in pure oxygen and mentions, but does not give the reference to, the work of Denny, Robson and Irwin[13] in 1939 on the inhibiting action of aluminum dust on silicosis and of Westerwick and co-workers who found somewhat the same effect with iron. If, however, we turn to the field of pharmacology there are many substances which, if not antagonists, are protective or antidotal agents. Well known examples are atropine and the nerve gases and EDTA and heavy metal poisoning.

Van Asperen[7] reports that the toxicity of the gamma isomer of benzene hexachloride is decreased by the presence of the less toxic alpha and delta isomers out of porportion to the percent of their diluting action. He refers to this phenomenon as *competitive inhibition*. The principal pharmacological action of the gamma isomer to stimulate the central nervous system. The beta and delta isomers are nervous system depressants and may partially eliminate the effects of the gamma isomer according to McNamara and Krop.[14] Ball and co-workers[15] have shown that when chlorinated hydrocarbon insecticides are administered several days ahead of organic phosphates animals can withstand eight times as much of the latter as can unprotected animals. This prophylactic action appeared to result from the chlorinated hydrocarbon's ability to elicit an overproduction of aliesterase which, successfully competing for the organic phosphate molecules, protected the more vitally important cholinesterase from inhibition.

While we can explain some observed examples of synergism or antagonism the diversity and complexity of joint action causes most toxicologists to avoid its theoretical aspects and we must turn for assistance to the work of the physiologists and entomologists.

In his monumental treatise, *Stress*, Selye[16] has emphasized that all stressors, whether physical, emotional or chemical, besides causing specific reactions, elicit non-specific responses. These responses, which are much the same no matter what the causative agent, he has designated the General Adaptation Syndrome (G-A-S). The first phase of the syndrome is the Alarm Reaction (A-R) which is characterized by such responses as increased adrenalin secretion and raised blood pressure. This is followed by the Adaptive Phase during which the body accommodates itself to the stress. Finally, under continued stress there may follow the Exhaustion Phase.

Because a great many dissimilar stresses may produce the same non-specific response it is not surprising that one stressor may so condition the body that the effect of another agent applied at the same time or subsequently will be greatly modified. Thus, while an organism becomes adapted to one systemic stressor its resistance to other agents is also altered. During the shock phase the non-specific resistance decreases even more than the specific resistance. In the counter-shock-phase, however, there is an increase in the animal's ability to withstand various systemic stressors besides that to which it has been exposed. This "non-specific resistance" Selye has called "crossed resistance". It is not, however, nearly as great as the resistance to the agent which triggered the A-R.

Selye mentions, as an example, that the lung edema normally produced by high doses of adrenalin is prevented in rats in which the A-R had been previously elicited either by adrenalin or by other systemic stressors (e.g. cold, exercise, formaldehyde).

The counterpart to crossed resistance—a decrease in tolerance to one agent produced by pretreatment with another agent—Selye designates "crossed sensitization". As an example, he states that after pretreatment with morphine resistance to atropine is reduced. Thus adaptation to one agent may be acquired at the expense of resistance to others.

While these theories of crossed resistance and crossed sensitization supply a physiological basis for the synergistic or antagonistic effects of multiple stressors, we still need a practical means of predicting the toxicity of specific mixtures. Here we can turn with advantage to work done by entomologists.

The development of quantitative methods for the estimation of toxicity has made it possible to determine the mode of action of jointly applied poisons by studying the curves relating dosage to percent kill or other index of toxicity. If the dose is transformed to logarithmus and the percentage kills to probits, the characteristic curve for each constituent of a mixture becomes a straight line. To find whether toxicity in enhanced or reduced when poisons are applied jointly in mixture, the percentage kill should be determined at several dosages. This procedure serves two purposes: (1) to determine whether the dosage-mortality curve is linear and (2)

to compute the amount required to kill, say 50% of the test organism. If the ratio of the constituents is kept constant and they do not react prior to application it is possible to recognize three principal types of joint action according to theory first developed by Bliss[17] and later refined by Finney.[18] The properties of these may be described as follows:

(1) *Similar Joint Action:* In similar joint action it is assumed that the components act upon the same system of receptors within the animal so that one can be substituted for another at constant ratio without changing the toxicity of the mixture.

(2) *Independent Joint Action:* In independent joint action the components are assumed to act at different reaction sites so that the effects produced are unrelated and the animal dies from one cause or the other rather than from the cumulative effect of the two poisons.

(3) *Synergistic or Antagonistic Joint Action:* In these types of joint action the effectiveness of the mixture cannot be assessed from that of the individual ingredients but depends upon a knowledge of their combined toxicity.

Similar Action

Poisons of related chemical constitution are likely to have similar joint action and show parallel regression lines. Their relative potency is, of course, the ratio of equally toxic doses (e.g. the LD_{50}'s).

The regression lines of two poisons may be written

$$\gamma_1 = a_1 + b \log \lambda \qquad (1)$$

$$\gamma_2 = a_2 + b \log \lambda \qquad (2)$$

λ is the dose, a_1 and a_2 constants and b the common slope of the lines; γ_1 and γ_2 are expressed as probits.

The potency of the second poison relative to the first is given by

$$\log p_2 = (a_2 - a_1)/b \qquad (3)$$

and equation (1) may be rewritten

$$\gamma_1 = a_1 + b \log (p_2\lambda)$$

Multiplication by the factor p_2 converts doses of the second into equivalent doses of the first, the kill then being predictable by means of equation (1). A mixture containing amounts $\lambda_1\lambda_2$ of the two poisons is said to show similar action if the kill is the same as that produced by a dose of the first equal to the sum λ_1 and $p_2\lambda_2$; thus similar action requires that the probit regression line for a mixture shall have the form

$$\gamma = a_1 + b \log (\lambda_1 + p_2\lambda_2) \qquad (4)$$

The concept of similar action and of equivalent doses may be extended to three or more poisons administered together.

Independent Action

In mixtures whose constituents act similarly any quantity of one can be replaced by an equitoxic amount of any other without altering potency. For a mixture whose constituents act independently the mortalities, not the doses, are additive. This type of action occurs with mixtures whose constituents produce their toxic effect in entirely different ways, e.g. a mixture of two insecticides one of which is a stomach poison and the other a contact poison.

Suppose that the doses of the two poisons in the mixture are capable of producing mortalities P_1 and P_2 respectively. If they act independently, a proportion P_2 of the test animals, which would survive the first poison, is expected to succumb to the second and the expected total mortality could be expressed by

$$P = P_1 + P_2(1 - P_1)$$

which can be rewritten and extended to three or more constituents as

$$P = 1 - (1 - P_1)(1 - P_2)\text{---}(1 - P_n)$$

Synergistic Action

Bliss'[17] definition of synergistic action was incomplete because it did not state if the normal action was to be considered similar or independent joint action. Finney[18] revised Bliss' equation with one which will distinguish the kinds of similar joint action and the degree of synergism that occurs. It may be written

$$\gamma = a + b \log (\pi_1 + p\pi_2 + K\sqrt{p\pi_1\pi_2}) + bx \qquad (5)$$

It is not as complex as might appear at first glance. π_1 and π_2 are the proportions of the two poisons and $x = \log_{10} \lambda$. A dose λ of the mixture produces the same effect as a dose

$$(\pi_1 + p\pi_2 + K\sqrt{p\pi_1\pi_2})\,\lambda$$

of the first constituent alone. Element K represents the amount of synergism.

If $K = 0$ the equation represents similar joint action. If K is positive the potency is greater than predicted by similar action, and the poisons have acted synergistically; if K is negative they have acted antagonistically. The constant K can

be called the "coefficient of synergism". The equation may be generalized to include mixtures of several toxic ingredients.

A possible reason why the treatment just discussed has not received wider consideration is that Bliss and Finney both stated that the theory applied only when the dosage-mortality data for the individual ingredients of a mixture could be expressed by parallel probit regression lines. Brieger[3] considered these techniques but dismissed them because of this limitation. Hewlett and Plackett[19] reported insecticidal compounds, very closely related chemically, which, when applied separately, give probit-log-dose lines of different slope. It appeared to them that the statistical treatment of similar joint action must, for this reason, be revised. These investigators chose to regard two poisons as acting similarly merely if they produced the response by causing the same system to react or fail and, if when applied jointly, neither poison influenced the behaviour of the other. They have proposed the following additional assumptions: (a) the amount, λ_1, of A reaching the site of action can be substituted at a constant proportion for that of B, λ_2, producing the same response when applied alone; (b) the minimum effective log-amounts acting are normally distributed with standard deviation $1/\theta$ for both poisons; and (c) the amounts of poisons A and B acting are related to the doses by

$$\lambda_1 = \mu_1 Z_1^{n_1}, \quad \text{and} \quad \lambda_2 = \mu_2 Z_2^{n_2}$$

When Z_1 and Z_2 are the doses of A and B respectively. From the definition of similar action and from (a) and (b) y (the probit response) is given by an equation of the form

$$y = \theta \log \left(Z_1^{b_1/\theta} h^{a_1/\theta} + Z_2^{b_2/\theta} h^{a_2/\theta}\right)$$

b_1 and b_2 are the slopes, h is the base of the log, a_1 and a_2 are constants.

These statistical treatments have been presented superficially and incompletely here merely to indicate the nature and potential of the method. The original papers should be consulted by serious workers.

In a private communication to the author Burchfield[20] also discounts the narrower interpretations of Bliss and Finney in these words, "I should also like to point out that I regard the interpretation of similar joint action given in

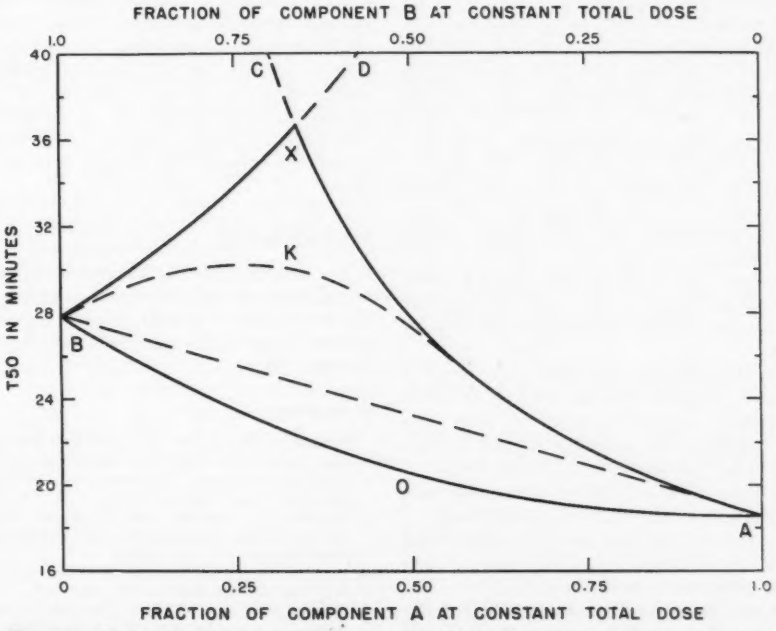

FIGURE 1. Illustration of independent and similar joint action of insecticides. AOB—similar joint action; AKB—independent joint action; AXC—change in T_{50} of component A with concentration; BXO—change in T_{50} of component B with concentration; AB—average value of T_{50} for a mixture.

TABLE I

Types of Joint Action Obtained on Various Binary Mixtures of Insecticides

Components of mixture	Action expected	Action found	Total test concentration in ppm
DDT-methoxychlor	Similar	Similar	0.1
DDT-heptachlor	Independent	Independent	0.1
DDT-chlordan	Independent	Independent	0.1
DDT-parathion	Independent	Similar	0.1
DDT-aldrin	Independent	Independent	0.05
Methoxychlor-heptachlor	Independent	Independent	0.1
Methoxychlor-chlordan	Independent	Independent	0.1
Methoxychlor-parathion	Independent	Independent	0.1
Parathion-malathion	Similar	Similar	1.0
Parathion-heptachlor	Independent	Similar	0.05
Heptachlor-chlordan	Similar	Similar	0.1
Parathion-aldrin	Independent	Independent	0.05
Heptachlor-aldrin	Indeterminate	Indeterminate	0.05
Aldrin-dieldrin	Similar	Similar	0.05

most entomological and statistical texts as being incorrect since it starts out with the assumption that the slopes of the dosage-response curves of two poisons having the same mode of action must be the same. This proposition is untenable for both theoretical and practical reasons."

Storrs and Burchfield[21] working with mosquito larvae have applied this theory to the prediction of the type of joint action found with a number of pairs of insecticides. In their experiments, T_{50} (time for 50% immobilization of the larvae) was plotted against concentration. The type of interaction in each case was arbitrarily decided by reference to a graph showing idealized cases of similar and independent joint action (Figure 1). The following criteria were used:

Mixtures which gave curves similar to *AOB* where all points were below the straight line *AB* were considered examples of similar joint action.

Pairs of insecticides for which part or all of the curve was above the line *AB* and on which a maximum usually exceeded *B* were considered examples of independent joint action.

Similarly, mixtures with points below *A* would have been considered synergistic and mixtures with points above *K* antagonistic.

The table shows that their prediction was wrong only twice in fourteen cases. No cases of synergism or antagonism were observed.

Storrs and Burchfield[21] point out that if the table is consulted, it will be seen that DDT and heptachlor, although both chlorinated hydrocarbons, exhibit independent joint action. These are not closely enough related structurally to act identically. Surprisingly, DDT and parathion do exhibit similar action even though very different structurally. However, DDT is known to increase the amount of free acetylcholine in nerve even though it does not inhibit cholinesterase *in vitro*. Parathion, on the other hand, is an effective inhibitor of cholinesterase and so both compounds increase the amount of acetylcholine although apparently by different mechanisms. These examples point out the danger of deciding what type of joint action exists without experimental evidence.

Storrs and Burchfield's application of the theoretical treatment of Bliss and Finney to a practical case suggests that toxicologists could with advantage look into these methods for the purpose of predicting the toxicity of mixtures encountered in their field.

Summary

The impracticability of experimentally determining the toxicity of all mixtures makes it imperative that theoretical approaches to the prediction of their toxicity be developed.

The first step is to consider the possible effects of chemical and physical interaction. Next, the broad principles of Selye's theories of combined stressors provide a starting point for the prediction of the physiological action of multiple poisons. Finally, the mathematical treatments of dosage-response curves developed by Bliss & Finney and used extensively by entomologists in predicting the effectiveness of insecticides will be found valuable to toxicologists who study mixtures.

Acknowledgment

The author wishes to express his appreciation of suggestions and references supplied by Dr. Hubert Martin, Director, Science Service Laboratory, Canada Department of Agriculture, London, Ontario.

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THE INSTITUTE OF INDUSTRIAL MEDICINE, New York University Post-Graduate Medical School has been presenting a series of courses relating to radiation and air pollution problems. Courses to be given in the near future are as follows:

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The Toxicological Basis of Threshold Limit Values: 5. The Experimental Inhalation of Vapor Mixtures by Rats, with Notes upon the Relationship between Single Dose Inhalation and Single Dose Oral Data*

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FREQUENTLY industrial hygienists and toxicologists are requested to estimate the toxicity or hazard of vapor mixtures. This study was initiated to determine the relationship between the inhalation LC_{50} values of composite vapors and the LC_{50} values of the individual components of these vapors. A considerable number of single dose oral LD_{50} values of chemical mixtures have been accumulated in this laboratory on female rats. Therefore, the relationship between the inhalation LC_{50} and oral LD_{50} values was also considered. The oral LD_{50} values of some 400 chemical mixtures will be the subject of a separate communication.

Methods

Groups of six female Carworth Farms-Nelson rats inhaled vapors of commercial chemical mixtures containing two to four components for a single 8-hour period. Similar groups of rats inhaled thirty-six pairs of vapors consisting of 50% of each component on a mg/liter basis for a single 4-hour period. The LC_{50} value, which represents the vapor concentration in mg/liter which would be expected to kill half of the animals, was calculated by the method of moving averages[1] for each commercial mixture and pair.

The vapors were produced by an elaboration of the apparatus described in a previous paper from this laboratory.[2] The liquid mixtures were delivered by a motor-driven syringe into a heated Pyrex evaporator through which an appropriate amount of air was metered.

The resultant vapors were then conducted into a 9-liter desiccator which served as the inhalation chamber for six rats. Components which were immiscible or were suspected of being reactive with each other in the liquid phase were delivered and vaporized separately (Figure 1). The bleeder rotameter was necessary to provide equal airflows containing equal concentrations of components A and B to the desiccator from each vaporizing system. For example, if the airflow containing 15 mg/liter of component A was 3 liters/min, and the airflow containing 15 mg/liter of component B was 4 liters/min, then one liter/min of the latter flow would be discharged through the bleeder rotameter. Vapor pairs containing acetonitrile, epichlorohydrin and propylene oxide were metered separately. All other vapor mixtures and vapor pairs were prepared in one vaporizing system.

The LC_{50} values of the individual components were determined and these were used in the following equation described by Finney to predict the LC_{50} values of the vapor mixtures or pairs in which they occurred.[3]

$$\frac{1}{\text{Predicted } LC_{50} \text{ Mixture}} = \frac{p_a}{LC_{50} \text{ Component } a} + \frac{p_b}{LC_{50} \text{ Component } b} \cdots + \frac{p_n}{LC_{50} \text{ Component } n}$$

where: p_a = Proportion of Component a
p_b = Proportion of Component b, etc.,
and $p_a + p_b \cdots + p_n = 1.00$

Assumed in the use of this formula are the qualifications that the components in a mixture have similar modes of action on the test animal and have parallel dosage response lines. These qualifications were not always satisfied with every mixture tested. The modes of action of the components in a given mixture were not always simi-

* Presented at the Twentieth Annual Meeting of the American Industrial Hygiene Association, Chicago, Illinois, April 25-May 1, 1959.

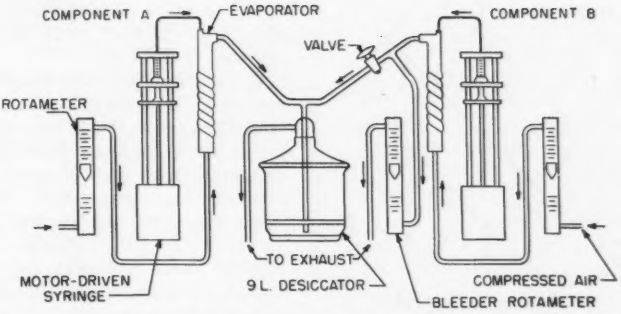

FIGURE 1. Apparatus for joint action of two vapors with separte liquid delivery.

TABLE I

Toxicities of Components of 15 Commercial Chemical Mixtures

Component	Code letter*	Single 8-hour inhalation, LC_{50} in mg/liter	Single oral, undiluted, LD_{50} in ml/kg
Acetone	a	50.1 (42.5 to 58.9)	12.6 (10.6 to 14.9)
n-Butyl acetate	b	40.6 (28.3 to 58.3)	14.9 (13.5 to 16.2)
Butyl alcohol	c	29.4 (26.3 to 33.0)	6.15 (5.51 to 6.87)
Butyl CELLOSOLVE	d	2.73 (0)	2.83 (2.19 to 3.65)
CELLOSOLVE	e	7.36 (4.01 to 13.5)	6.15 (5.51 to 6.87)
CELLOSOLVE acetate	f	12.1 (9.1 to 16.1)	7.71 (6.24 to 9.53)
Ethylene dichloride	g	4.04 (2.20 to 7.42)	0.62 (0.53 to 0.71)
Isobutanol	h	18.4 (15.6 to 21.6)	6.16 (5.52 to 6.88)
Isopropanol	r	27.7 (0)	10.7 (9.3 to 12.4)
Isopropyl acetate	j	50.6 (43.0 to 59.5)	17.2 (12.2 to 23.2)
Methanol	k	59.3 (0)	17.8 (0)
Methyl ethyl ketone	l	23.5 (12.8 to 43.2)	6.86 (5.59 to 8.45)
Methyl isobutyl ketone	m	11.6 (0)	5.66 (0)
Perchlorethylene	n	34.2 (22.7 to 51.5)	1.62 (0.94 to 2.80)
Propylene dichloride	s	14.0 (11.9 to 16.5)	1.68 (1.48 to 1.91)
1,1,2-Trichloroethane	p	5.45 (2.97 to 10.0)	0.58 (0.47 to 0.71)

* These code letters are used to describe the composition of the various mixtures in Table II.

lar, nor were enough animals used per dosage level to establish that the slopes of the dosage response lines were parallel. Therefore, this calculation was used merely as a benchmark which furnished a rough prediction of the LC_{50} value of a vapor mixture.

Results

The LC_{50} values of the individual components of the 15 commercial chemical mixtures and of the mixtures themselves are shown in Tables I and II respectively.

The similarity of mixtures 13 and 14 was not realized at the time of testing, but this oversight served to indicate the high degree of reproducibility of results. The relationship between the predicted and observed LC_{50} values of the 15

TABLE II

Predicted and Observed LC_{50} and LD_{50} Values of 15 Commercial Chemical Mixtures

Mixture number	Percentage by weight and component identification*				Single 8-hour inhalation, LC_{50} in mg/liter		Single oral, undiluted, LD_{50} in ml/kg	
					Predicted	Observed	Predicted	Observed
1	a-75.0	k-25.0			52.1	56.6	13.6	11.9
2	k-50.2	r-49.8			37.8	33.6	13.4	14.8
3	e-67.0	d-33.0			4.72	3.30	4.43	5.16
4	a-85.1	r-14.9			44.7	33.6	12.3	9.32
5	c-85.0	h-15.0			28.8	28.3	6.15	7.48
6	b-52.4	m-47.6			18.5	28.3	8.38	10.4
7	a-76.5	f-23.5			28.8	28.3	11.0	17.8
8	s-61.6	p-38.4			8.74	5.00	0.97	1.00
9	g-78.3	n-13.0	s-8.7		4.91	7.07	0.72	0.73
10	c-33.5	l-33.4	m-33.1		18.5	28.3	6.19	7.06
11	b-61.6	c-28.2	j-10.2		38.5	40.0	10.7	12.3
12	m-66.2	r-22.8	c-11.0		14.6	20.0	6.40	5.66
13	b-43.5	j-25.4	c-21.8	r-9.3	37.7	52.8	11.4	19.2
14	b-44.7	j-22.4	c-20.7	r-12.2	37.2	56.6	11.4	17.0
15	a-46.8	f-28.7	r-15.6	d-8.9	14.0	26.4	8.31	10.5

* Code letters are explained in Table I.

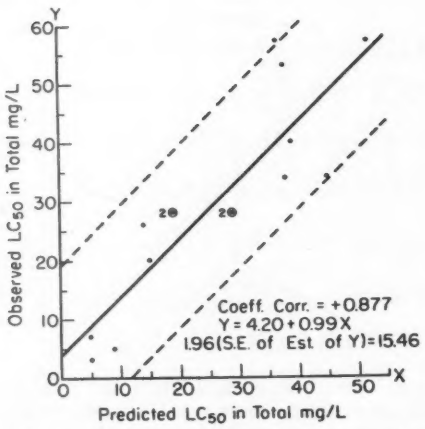

FIGURE 2. Relationship between observed and predicted LC_{50} values of 15 commercial vapor mixtures inhaled by rats for eight hours.

mixtures is shown in Figure 2. The coefficient of correlation was relatively high, + 0.877. The regression equation, $Y = 4.20 + 0.99X$, is an expression of the line of best fit for the data, which is shown as the solid line. It indicates the average value for Y (the observed LC_{50}), when one substitutes values for X (the predicted LC_{50}). As an example, if one predicted the LC_{50} value of a vapor mixture, using the previous equation, to be 30 mg/liter, one would expect the observed LC_{50} to be 33.90 mg/liter. The dispersion of values around the line of best fit is given by 1.96 times the standard error of estimate of Y which is indicated by the two dashed lines. In this case 15.46 is added and subtracted from 33.90. Therefore, one would expect the actual observed value for a predicted LC_{50} of 30 mg/liter to fall between 18.44 and 49.36 ninety-five per cent of the time.

If one wishes to think in terms of "potentiating" and "antagonistic" action between the components of a mixture, one could consider the points below the lower dashed line on this graph as representing mixtures whose components are "potentiating" each other, and those points above the upper dashed line as "antagonistic" action. We prefer to use the terms "more than additive" and "less than additive" for we feel they are less equivocal than the terms "potentiating" and "antagonistic". The point above the dashed line in Figure 2 represents mixture 14 and indicates that the components tend to exert a less than additive effect upon each other. It should be pointed out that the individual LC_{50} values of the components were not determined on the same lots of chemicals that were used to prepare the liquid mixtures.

The 36 chemical pairs of vapors investigated in the second series of joint action studies were prepared from the same lots of components on which LC_{50} values were determined. The inhalation periods were of four hours duration and the vapor pairs consisted of 50% of each component on a mg/liter basis.

The LC_{50} values of the components of the 36 vapor pairs are presented in Table III and the predicted and observed LC_{50} values of the pairs themselves are presented in Table IV.

Figure 3 shows the relationship between the predicted and observed LC_{50} values of the 36 vapor pairs, and again a rather high coefficient of correlation is evident. Note again the dashed lines between which 95% of the values may be expected to fall. Reading from left to right, the two points beneath the lower dashed line in Figure 3 represent the acetonitrile-acetone and the carbon tetrachloride-hexane pairs respectively. These two pairs may be said to show a tendency toward more than additive effects.

Some interesting relationships between the inhalation LC_{50} values and the oral LD_{50} values were obtained for the same components and mixtures. It was reasoned that if the correlation between single dose oral and inhalation data was sufficiently high and if LD_{50} values for only one route were available, those for the other route might be predicted with a reasonable amount of reliability.

The oral LD_{50} values of the components of the 15 commercial mixtures are shown in Table I, and the oral LD_{50} values of the mixtures in which these components occurred are shown in Table II. The coefficient of correlation between the predicted and observed LD_{50} values of the 15

TABLE III

Toxicities of Components of 36 Vapor Pairs Inhaled by Rats and of 23 Chemical Pairs Administered Orally

Component	Single 4-hour inhalation, LC_{50} in mg/liter	Single oral, undiluted, LD_{50} in ml/kg
Acetone	76.0 (65.2 to 88.4)	12.6 (10.6 to 14.9)
Acetonitrile	26.9 (21.9 to 33.0)	8.27 (6.41 to 10.68)
Carbon tetrachloride	38.1 (32.5 to 44.8)	3.08 (2.47 to 3.83)
Dioxane	51.3 (48.5 to 54.3)	6.16 (4.69 to 8.08)
Epichlorohydrin	1.25 (1.09 to 1.45)	0.16 (0.11 to 0.25)
Ethyl acetate	40.7 (35.0 to 47.4)	10.9 (9.1 to 13.1)
Hexane	148.6 (126.3 to 174.9)	*
Propylene oxide	7.74 (5.14 to 11.59)	0.54 (0.35 to 0.83)
Toluene	19.0 (12.5 to 28.8)	9.13 (8.29 to 10.04)

* The oral toxicity of hexane was too low (>100 ml/kg), to yield a reliable LD_{50} value.

TABLE IV
Predicted and Observed LC_{50} and LD_{50} Values of 36 Vapor Pairs Inhaled by Rats and of 23 Chemical Pairs Administered Orally

Chemical pairs	Single 4-hour inhalation,* LC_{50} in mg/liter		Single oral, undiluted,† LD_{50} in ml/kg	
	Predicted	Observed	Predicted	Observed
Acetone + Hexane	100.7	123.4	—	—
Dioxane + Hexane	76.3	119.4	—	—
Ethyl acetate + Hexane	63.9	90.4	—	—
Acetone + Dioxane	61.2	61.6	8.28	7.13
Carbon tetrachloride + Hexane	60.6	35.6	—	—
Acetone + Ethyl acetate	53.0	68.1	11.7	12.9
Acetone + Carbon tetrachloride	50.8	61.2	4.78	3.73
Acetonitrile + Hexane	45.6	74.1	—	—
Dioxane + Ethyl acetate	45.4	84.4	7.87	11.3
Carbon tetrachloride + Dioxane	43.7	56.6	4.50	3.73
Acetonitrile + Acetone	39.7	14.6	9.99	2.75
Carbon tetrachloride + Ethyl acetate	39.4	56.6	4.64	11.2
Acetonitrile + Dioxane	35.3	23.5	7.06	2.24
Hexane + Toluene	33.7	47.6	—	—
Acetonitrile + Ethyl acetate	32.4	51.4	9.40	14.1
Acetonitrile + Carbon tetrachloride	31.5	45.5	4.35	6.77
Acetone + Toluene	30.4	37.3	10.59	7.96
Dioxane + Toluene	27.7	40.2	6.75	7.46
Ethyl acetate + Toluene	25.9	55.5	9.94	18.7
Carbon tetrachloride + Toluene	25.4	22.4	4.46	2.95
Acetonitrile + Toluene	22.3	44.4	8.68	3.73
Hexane + Propylene oxide	14.7	24.3	—	—
Acetone + Propylene oxide	14.0	20.5	1.04	2.38
Dioxane + Propylene oxide	13.4	20.1	0.99	1.42
Ethyl acetate + Propylene oxide	13.0	19.8	—	—
Carbon tetrachloride + Propylene oxide	12.9	9.9	0.91	0.84
Acetonitrile + Propylene oxide	12.0	25.8	1.01	1.83
Propylene oxide + Toluene	11.0	16.6	1.02	1.41
Epichlorohydrin + Hexane	2.48	2.60	—	—
Acetone + Epichlorohydrin	2.46	1.84	0.32	0.26
Dioxane + Epichlorohydrin	2.44	1.96	0.31	0.35
Carbon tetrachloride + Epichlorohydrin	2.42	1.82	—	—
Epichlorohydrin + Ethyl acetate	2.42	3.65	—	—
Acetonitrile + Epichlorohydrin	2.39	2.25	—	—
Epichlorohydrin + Toluene	2.34	1.96	—	—
Epichlorohydrin + Propylene oxide	2.15	3.25	0.25	0.43

* The 36 vapor pairs consisted of 50–50 mixtures on a mg/liter basis.

† The 23 chemical pairs orally administered to rats consisted of 50–50 mixtures on a v/v basis.

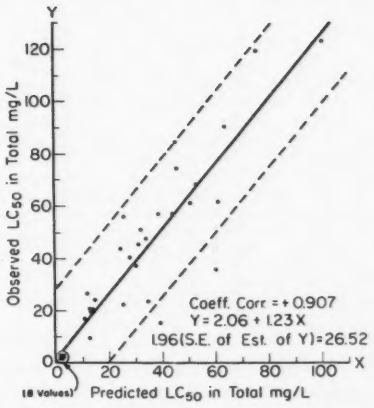

FIGURE 3. Relationship between observed and predicted LC_{50} values of 36 vapor pairs inhaled by rats for four hours.

mixtures administered orally was calculated to be +0.858, with a regression equation of $Y = 0.21 + 1.18X$ and 1.96 times the standard error of estimate of $Y = 5.53$. Mixture 13 fell just above the 95% zone and showed a tendency toward less than additive action.

The LD_{50} values of the components of the 23 chemical pairs administered orally are shown in Table III, and the LD_{50} values of the pairs in which these components occurred are shown in Table IV. The coefficient of correlation between the predicted and observed LD_{50} values of the 23 chemical pairs was calculated to be +0.724 with a regression equation of $Y = 0.54 + 0.95X$ and 1.96 times the standard error of estimate of $Y = 6.76$. The ethyl acetate-toluene pair exhibited a tendency toward less than additive action and the acetonitrile-acetone pair exhibited a tendency toward more than additive action.

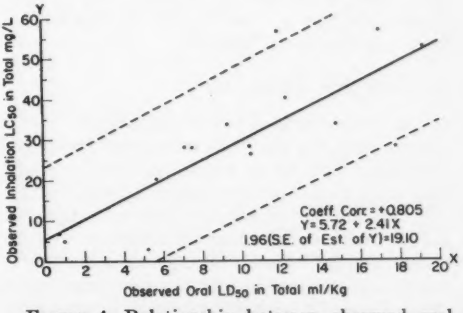

FIGURE 4. Relationship between observed oral LD_{50} values and observed inhalation LC_{50} values of 15 commercial chemical mixtures.

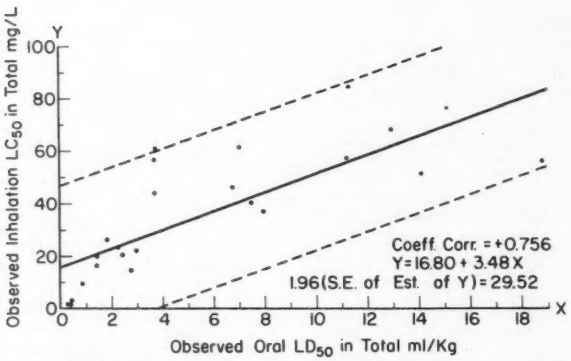

FIGURE 5. Relationship between observed oral LD_{50} values and observed inhalation LC_{50} values of 23 chemical pairs.

TABLE V

Summary of the Relationships Between Predicted and Observed Joint Action Data by Respiratory and Oral Routes

X vs. Y	No. of mixtures or pairs	Coefficient of correlation	(1.96) Standard error of estimate of Y	Regression equation
Mixtures				
Predicted inhalation vs. Observed inhalation	15	+0.877	15.46	$Y = 4.20 + 0.99X$
Predicted oral vs. Observed oral	15	+0.858	5.53	$Y = 0.21 + 1.18X$
Observed oral vs. Observed inhalation	15	+0.805	19.10	$Y = 5.72 + 2.41X$
Observed oral vs. Observed inhalation	*	+0.836	—	—
Pairs				
Predicted inhalation vs. Observed inhalation	23	+0.826	—	—
Predicted inhalation vs. Observed inhalation	36	+0.907	26.52	$Y = 2.06 + 1.23X$
Predicted oral vs. Observed oral	23	+0.724	6.76	$Y = 0.54 + 0.95X$
Observed oral vs. Observed inhalation	23	+0.756	29.52	$Y = 16.80 + 3.48X$
Observed oral vs. Observed inhalation	†	+0.721	—	—

* 16 Components
† 8 Components

The latter pair also had a tendency towards more than additive action upon inhalation.

The relationship between the observed inhalation LC_{50} values and the observed oral LD_{50} values of the 15 commercial chemical mixtures are shown in Figure 4, and that for the 23 chemical pairs are shown in Figure 5.

Summary and Conclusions

The components of the 15 commercial chemical mixtures and the 36 chemical pairs tested did not in any case act in a markedly less or markedly more than additive manner by the respiratory route. This observation was also true for the 15 commercial chemical mixtures and 23 chemical pairs tested orally. The acetone-acetonitrile and the carbon tetrachloridehexane pairs showed a slight tendency to act in a more than additive manner by inhalation (Table IV, Figure 3), as was also true for the acetone-acetonitrile pair by oral administration, Table IV.

The ethyl acetate-toluene pair tended to act in a slightly less than additive manner orally, Table IV. All of the values of the above pairs fell outside of the 95% dispersion zone described by the value, 1.96 times the standard error of estimate of Y, but it must be recalled that even if all of a large number of chemical mixtures acted in a strictly additive manner, one would still expect 5% of the values to lie outside of the "dispersion" zone.

The various comparisons discussed previously are summarized in Table V.

The highest correlations were found between the predicted inhalation and observed inhalation values. However, the lower but still significant correlations between the observed oral and observed inhalation values suggest that one can

estimate a single dose inhalation LC_{50} value from oral data with a fair amount of reliability.

The limited quantity of data presented in this paper indicate that although the formula used to predict the LC_{50} and LD_{50} values of chemical mixtures is theoretically suitable only for similar joint action, it provided a fairly accurate method for predicting the single dose toxicity of mixtures from the single dose toxicity data of their components.

The authors are indebted to Miss Jean Striegel and Mr. Charles Haun for their able assistance in this work.

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Personal Fallout Detector

A SELF-CONTAINED, low cost detector and alarm for radioactive fallout has been developed by Controls for Radiation, Inc. The new device, called "FIDO", is designed to give protection in the event of nuclear attack or other such radiation accident. "FIDO" emits an audible signal that increases in intensity as radiation rises above 0.2 roentgens per hour. A meter may replace the sound signal for visual reading. Fully transistorized, the instrument operates on batteries and is reported to respond to all forms of nuclear radiation at dose rates up to 5,000 roentgens per hour. Such an instrument, when available, should find many uses in industrial hygiene.

New Candlepower Standards

NEW PHOTOMETRIC STANDARDS for measuring the candlepower or luminous intensity of electric lamps are now available from the Photometry and Colorimetry Section, National Bureau of Standards, Washington, D.C. These standards consist of inside-frosted lamps with monoplane filaments and medium-bipost bases. They are available in 100-, 300-, and 500-watt sizes. These standards show little or no variation in intensity with changes in orientation, follow closely the inverse square law, are easily oriented on a photometer bar, and need no diaphragm when being used to calibrate photometers or other lamp standards.

The Toxicological Basis of Threshold Limit Values: 6. Report of Prague Symposium on International Threshold Limit Values

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THE INTERNATIONAL Symposium on Maximum Allowable Concentrations of Toxic Substances in Industry was held in Prague, Czechoslovakia April 14–17, 1959, under the auspices of the Permanent Committee and International Association on Occupational Health and the International Union for Pure and Applied Chemistry. The symposium was attended by some 125 scientists from 22 countries. The organizing committee was composed of: Prof. Rene Truhaut (Paris), President; Prof. Jaroslav Teisinger (Prague), General Secretary; Prof. Sven Forssman (Stockholm); Prof. Etienne Grandjean (Zurich); and Prof. Enrico Vigliani (Milan).

All papers were by invitation from the organizing committee. At the symposium they were translated simultaneously into English, French and Russian.

The subject was treated under four sections by one or two main reports followed by a number of communications.

Section I

The investigation of present time definitions and conceptions of maximum allowable concentrations in different countries.

The main paper, *Basic Conceptions in the Field of Maximum Allowable Concentrations,* was delivered by Prof. A. A. Letavet, Director of the Institute of Industrial Hygiene in Moscow. Twelve communications, including papers by Dr. Harriet Hardy of Boston and myself completed the formal presentation. The meeting was then opened to discussion from the floor.

A subcommittee, of which I was chairman, was requested to prepare a report and resolutions based on the papers and discussion. This was presented at the end of symposium for adoption by the meeting. It was felt that more time to consider the resolutions should be allowed and they were distributed to all registered at the symposium for comments. The following resolutions as modified by the comments received will be incorporated into the transactions of the symposium:

General principles relating to maximum allowable concentrations of toxic substances in industrial atmospheres

1. Since the international adoption of uniform values of maximum allowable concentrations of toxic substances in the environment of work areas would be most beneficial, this symposium recommends the preparation and continuing revision of tables of "maximum allowable concentrations" by the Subcommittee of the Permanent International Commission of Industrial Medicine and that these values be based on the most reliable information available in all countries.
2. This symposium recommends that the term "maximum allowable concentration" for any substance shall be that value which leads to no significant aberrations from normal, as judged by the most sensitive of known indices of toxicity, of all except hypersensitive workers exposed to such agent be it gas, vapour, dust or other during their normal working day and on a continuing basis.

   When significant discomfort occurs at concentrations of agents in the environment below the MAC selected on the basis of toxicity it may be advisable to lower this value.
3. Special consideration should be given to the application of MACs when exposure to combinations of two or more substances occurs. The effect of other environmental conditions must be considered.
4. MACs should be used only as guides in the control of health hazards and should not be regarded as a fine line between safe and dangerous concentrations and they should be applied only by persons trained in industrial hygiene.
5. When exposure concentrations exceed the MAC values for limited periods in any working day without causing the average to be too high, the decision as to whether a health

hazard exists should be based on a consideration of such factors as the nature of the material, whether the effects are cumulative, the frequency with which high concentrations occur, and the duration of such concentrations.

6. All MAC values proposed by the committee charged with issuing such tables should be based on documented scientific evidence, whether animal experimentation or human experience.
7. In the interest of securing the maximum protection of the health of working people, MAC values should be applied to the greatest extent possible.
8. This symposium recommends that the committee charged with drawing up MAC tables for international use should maintain close contact with such agencies as the Internationa Labour Office and the World Health Organisation.

Section II

The evaluation of present time methods and procedures used in different countries for the determination and fixing of maximum allowable concentrations.

The first main paper, *Experimental Methods Used as a Basis for Determining Maximum Allowable Concentrations*, was presented by Dr. J. M. Barnes of the Medical Research Council of Great Britain. The second, *Some Methods Which are Used for Determination of Maximum Allowable Concentrations*, was presented by Dr. Elizaveta Lublina of the Institute of Industrial Hygiene, Moscow. Seventeen communications, including those by Dr. Deichmann of Miami, Dr. Kehoe of Cincinnati and Dr. von Oettingen were delivered.

After discussion from the floor a report was prepared by a committee with Dr. Barnes as chairman. The text of this report is transcribed here:

METHODS USED TO PROVIDE THE INFORMATION NEEDED IN ORDER TO PROPOSE AN MAC

1. Papers presented to the symposium showed that various countries have used different methods in order to provide the information needed to set up MAC values. The use of these different research procedures often gave results that were not in complete agreement.
2. Because of the differences in the physical, chemical and biological properties of the toxic substances to be examined, the symposium considers that it is not possible nor indeed desirable to standardize the methods of investigation used in the study of toxicity.
3. The following general recommendations based on the experiences in different countries can be made:
   (a) Experimental studies on animals by well known, generally accepted methods should be used to establish the acute, cumulative and chronic toxic effects and general mode of action of a substance. This work will indicate the general category of poison to which the substance belongs.
   (b) Further experimental work is necessary to establish more precisely the toxicity of a material. This will necessitate the use of the techniques of biochemistry, physiology and pathology. The information sought will include the metabolism and excretion of a substance. Of special interest are methods involving the study of the functional state of the central nervous system including the study of conditioned reflexes.
   (c) People who work in industry must be studied periodically by appropriate clinical and epidemiological methods. These studies must be coordinated with determinations of the conditions of work including exposure to toxic substances and potentially harmful stresses. Such work should be carried out methodically so as to make use of satisfactory technical and statistical methods.
4. The symposium considers it essential that international cooperation on work relating to proposed values shall be actively fostered and requests the committee:
   (a) to obtain the relevant information on the work carried out in different countries related to the establishment of MAC values, and (b) to publish the values proposed in different countries indicating the methods used to arrive at the decisions made.

Section III

Maximum allowable concentrations in biological materials.

The first principal paper, delivered by Prof. Rene Truhaut of the University of Paris was *Maximum Allowable Concentrations in Biological Materials—Analytical, Biochemical and Pharmacological Aspects*. The second principal paper was delivered by Prof. Jaroslav Teisinger, Director of the Institute of Industrial Hygiene and Occupational Diseases, Prague, and was entitled *Biological Tests of Absorption*. Among the thirteen communications was one by Dr. Hervey Elkins of Boston. Dr. Truhaut was

chairman of the committee which summarized the proceedings.

The text of the report which was presented to the meeting was as follows:

MAXIMAL ALLOWABLE CONCENTRATIONS IN BIOLOGICAL MATERIAL

1. The symposium considers that the analysis of biological material, for example, blood, urine and expired air, is of great importance in the diagnosis and prevention of occupational diseases due to various industrial poisons and that the establishment of maximal allowable concentrations in biological material, analogous to those in air, would be of great interest.
2. Industrial toxic substances may be divided into two groups: those which are normally absent from the body and those which are normally present in small quantities such as lead, mercury, fluorine and arsenic. It is considered important to establish the range of concentrations of the latter group in the tissues of the general populations in different countries so that the effects of industrial exposures may be correctly evaluated.
3. The symposium has considered the distribution and excretion of arsenic, cadmium, fluorine, carbon monoxide, manganese, mercury and lead, and recommends that the subcommittee of the Permanent International Commission of Industrial Medicine should collect information and stimulate research so that maximum allowable concentrations can be adopted for these and other important inorganic substances.
4. The symposium stresses the importance of the metabolic transformation which may take place with organic substances and has considered the following:—benzene to phenol, toluene to benzoic acid, trichlorethylene to trichlorethanol and trichloracetic acid, nitrobenzene and aniline to p-aminophenol, DDT to DDA, and parathion to p-nitrophenol. It is recommended that all the available information on these and other important transformations should be collected as soon as possible.
5. The symposium is of the opinion that careful attention should be given to the selection of methods for the determination of toxic substances and their metabolites in biological material. It recommends that the International Union of Pure and Applied Chemistry should be asked to entrust such a study to its Division of Toxicology and Industrial Hygiene and also to maintain the necessary relations with the Subcommission for the Study of Maximal Allowable Concentrations in Industry of the Permanent International Commission for Industrial Medicine.

Section IV

The evaluation of the importance of suitable methods of chemical analysis, physical methods and methods of sampling used in industry.

The main report, *Analytical Methods for Measuring the Concentration of Toxic Substances in Industrial Atmospheres*, was delivered by Dr. J. C. Gage, Imperial Chemical Industries, Great Britain. Six communications completed the formal presentation.

The report on this section as presented by a committee with Dr. Gage as chairman follows:

THE IMPORTANCE OF SUITABLE METHODS OF PHYSICAL OR CHEMICAL ANALYSIS

1. If any toxic substance is used in a factory or workshop which may cause atmospheric contamination, this fact should be known by the responsible authority. They should also be aware of the nature and amount of any toxic impurities in the material used.
2. Regular air analyses are probably the best method of evaluating atmospheric contamination. As the concentration of a toxic substance in a factory atmosphere will vary in space and time, the design of such tests should be supervised by a person conversant with the local conditions, and the results interpreted by a person familiar with the toxic properties of the substances present.
3. The selection of suitable analytical methods should be undertaken by analysts in collaboration with industrial toxicologists. It is very desirable to keep the methods simple and a high degree of precision is not essential, results within ±20% being adequate. It is, however, essential that the agreed degree or precision should be attainable in the region of the maximal allowable concentration, however low this figure may be. From an analytical point of view, it is undesirable that the maximal allowable concentration should be set at zero, as precision has no meaning at this level.
4. The Toxicology and Industrial Hygiene Division of the International Union of Pure and Applied Chemistry is an organization undertaking the publication of methods for the determination of toxic substances in air, which have been selected by international

experts. It is recommended that all other national or international organizations with similar interests should collaborate with the IUPAC Division to exchange information and experience.

Another symposium on maximum allowable concentrations will be held under the auspices of the Thirteenth International Congress on Occupational Health which will meet in New York City, July 25–29, 1960.

Impressions of the Symposium

One was struck with the spirit of co-operation, understanding and singleness of purpose which was evident.

While Russian block scientists have relatively little personal contact with outside researchers they appear to be better informed on western work than we are on theirs. They spoke of maximum allowable concentrations values which were often only one tenth of those generally accepted in America. They claim to be able to detect the effect of such low levels of toxicant by observing changes in the central nervous system. Their use of the conditioned reflex which is familiar to many from the classical work of Pavlov on dogs deserves more serious consideration. Against the claim that an animal is not really sick if there are no detectable clinical variations from normal, the Russians point out that even a slight slowing of reflexes can be dangerous to industrial workers.

The annually issued lists of threshold limit values prepared by the American Conference of Governmental Industrial Hygienists appear to be the most widely accepted values in the world and are considered to be the official American figures.

Considerable attention was given to maximum allowable concentrations of toxic chemicals or their metabolites in biological materials. In America, while tentative values have been proposed for a few excretion products, it doesn't appear that the subject has received as much attention as in Europe.

Symposium on Inhaled Particles and Vapours

THE BRITISH OCCUPATIONAL HEALTH SOCIETY has organized a Symposium on Inhaled Particles and Vapours to be held at Oxford, England, March 29–April 1, 1960. Papers are planned in the following major areas: (1) Anatomy and Physiology of the Respiratory Tract, (2) Distribution and Retention of Particles and Vapours in the Respiratory Tract, (3) Elimination of Materials from the Respiratory Tract, (4) Reactions with the Respiratory Tract arising from the Presence of Particles and Vapours, (5) Sampling Techniques Simulating Respiratory Retention.

Attendance must be limited to 250 and those who wish to attend are advised to signify their intention as soon as possible. For further details, final program, and registration, address Dr. J. S. McLintock, Medical Service, National Coal Board, Hobart House, London, S.W.1.

The Collection and Infrared Analysis of Low Molecular Weight Hydrocarbons from Combustion Effluents*

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Introduction

IN RECENT years much attention has been focused on the role played by hydrocarbons in the atmosphere in the formation of photochemical smog.[1, 2, 3] Sources of hydrocarbon emissions to the atmosphere include automobile exhaust, refinery operations, incineration, combustion of fuel oil and gas and many other industrial operations. This paper in concerned with the collection and analysis of hydrocarbons from incineration and combustion sources.

Methods for the estimation of other types of pollutants from these sources have appeared in the literature[4, 5] and some attention has been paid to the measurement of hydrocarbons.[6, 7, 8] Quantitative measurements of hydrocarbons have been reported by Yocom,[7] Rose,[9] and others.[4, 8, 10, 11]

Apparatus and Equipment

1. Beckman IR4 Spectrophotometer
2. Beckman Variable Path Ten-meter Cell
3. Hensen Quick-Connect Couplings
4. Thirty-five-liter stainless steel tanks
5. Gases, Matheson, 99 per cent purity
6. Ascarite
7. Tygon tubing

The method to be described is based upon the infrared absorption of hydrocarbons in a gas cell with a ten-meter path. The sensitivity achieved with the use of such a long path gas cell permits the direct analysis of low concentrations of hydrocarbons from combustion effluents without the necessity of a concentration step by freeze-out or other techniques.

Collection Procedure

Samples of effluent are collected in stainless steel tanks equipped with vacuum gauges. A millipore or glass fiber filter is inserted between the tank and the stainless steel sampling probe to prevent particulate material from entering the tank. Samples are drawn into the previously evacuated tank by opening the valve and observing the vacuum gauge. In this fashion an integrated gas sample can be collected over as long a period of time as is desired. The usual practice has been to use 35-liter tanks and to collect samples over a 5–10 minute period. Collection is complete when the vacuum gauge reads zero. When the gases in the tank have cooled to room temperature the vacuum gauge is again read, and a correction applied for the contraction in volume caused by cooling of the hot effluent gases.

Analytical Procedure

The tank is then connected to the evacuated gas cell and the contents are permitted to slowly enter the gas cell through an ascarite trap. At equilibrium the pressure within the cell is read from a mercury manometer connected to the cell. The tank is removed and the pressure within the cell is brought to atmospheric by admitting CO_2-free, dry air through an ascarite trap. The spectrum is then recorded from 2-15 microns.

Calibration

Calibration of the instrument with known quantities of gas is accomplished as follows: The amount of gas required to give a 250 ppm (v/v) concentration in the 3.85-liter gas cell is measured into a luer-lok syringe from a tank of pure gas. The contents of the syringe are injected into the evacuated gas cell through a serum cap, using a 26-gauge hypodermic needle. The cell is filled to atmospheric pressure with CO_2-free, dry air and the spectrum of the gas is recorded. Dilutions are made by partially evacuating the cell, noting the pressure and refilling to atmospheric pressure with CO_2-free,

* Presented at the Twentieth Annual Meeting of the American Industrial Hygiene Association, Chicago, Illinois, April 25–May 1, 1959.

dry air. The new concentration is computed as follows:

$$\text{Concentration (ppm)} = \text{original concentration} \times \frac{\text{observed pressure}}{\text{atmospheric pressure}}$$

A graph relating concentration to absorbance at the appropriate wavelength is constructed for each gas. Absorbances are measured by the base line technique.[12]

For vapors of hydrocarbons normally existing as liquids the procedure for calibration is somewhat similar. Weighed quantities of liquid are delivered into a flask of known volume. The flask is sealed and the sample is completely vaporized and mixed. An aliquot is withdrawn from the flask with a syringe and needle through a serum cap and injected into the gas cell. The procedure following is similar to that described for gases. Table I shows the limit of sensitivity obtained with the ten-meter gas cell for a series of hydrocarbons.

TABLE I

Limit of Sensitivity for Hydrocarbons Using Ten-meter Gas Cell

Compound	Absorption peak (microns)	Limit of sensitivity (ppm)
Methane	7.63	2
Acetylene	13.7	1
Ethylene	10.53	2
Ethane	3.4	3
Propane	3.4	3
Propylene	10.96	4
Butene-1	10.96	6
Butane	3.4	2
Pentane	3.4	2
Hexane	3.4	2

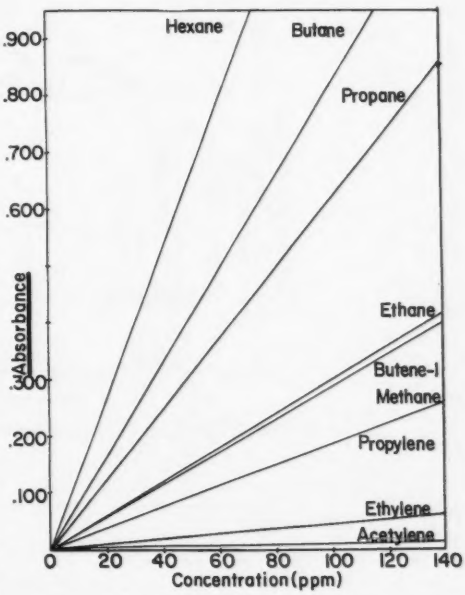

FIGURE 1. Absorbance of hydrocarbons at 3.4 microns (ten-meter path gas cell).

Discussion

It is well known that all hydrocarbons absorb in the 3.4 micron region of the infrared spectrum. Unfortunately, the absorbance for equal concentrations of hydrocarbons is not the same, and varies with the chemical structure of the material. This is clearly shown in Figure 1 where the absorbance of a series of low molecular weight hydrocarbons is plotted against concentration. At part per million concentrations the spectra of ethane, propane, butane, pentane and hexane are quite similar and the 3.4 micron peak is common to all. The choice of a suitable standard to represent total hydrocarbon concentration thus becomes a difficult matter. Most reports in the literature use hexane as a standard.

Inspection of Figure 1 indicates that an absorbance of 0.100 for eight parts per million hexane would represent the following concentrations of other low molecular weight hydrocarbons:

Methane	51	ppm
Ethane	33	"
Propane	16	"
Butane	12	"
Pentane	11	"

It would thus be difficult to assess the total hydrocarbon concentration of an unknown mixture of these gases if only the total absorbance at 3.4 microns were used. In addition, the contribution to the 3.4 micron peak by parts per million concentrations of ethylene and acetylene is negligible.

It should be pointed out that the major types of low molecular hydrocarbons emitted by combustion and incineration processes and collected by the procedure described above, consist of C_1 to C_5 saturated and unsaturated compounds. Some of those compounds can be identified and measured from absorption peaks in other areas of the spectrum. Table II lists those compounds and the characteristic absorption peaks associated with them. It should be remembered that

TABLE II

Characteristic Absorption Peaks of Low Molecular Weight Hydrocarbons

Compound	Absorption peak (microns)
Acetylene	13.71
Methane	7.63
Ethylene	10.53
Propylene	10.96, 10.05
Butene-1	10.96

when parts per million concentrations of organic compounds are measured in the infrared region of the spectrum, only the most intense absorption peaks are recorded. Most of the less intense peaks appear only at much higher concentrations. At the higher concentrations, differentiation between ethane, propane and butane may readily be accomplished.[13] Figures 2, 3, 4 and 5 show the characteristic spectra in the parts per million concentration range for several combustion effluents and for mixtures of methane, acetylene, ethylene, propylene and butene-1.

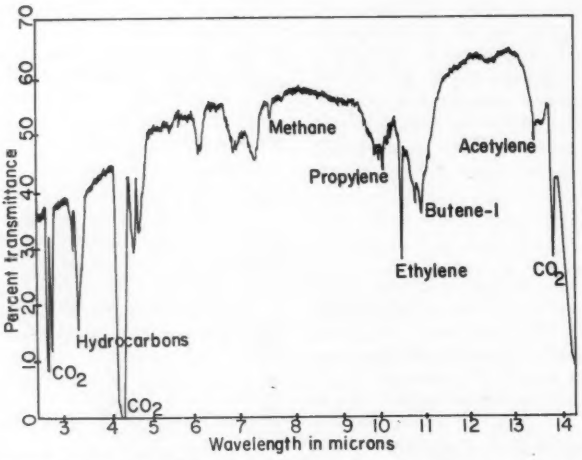

FIGURE 2. Incinerator effluent (single chamber) (ten-meter path gas cell).

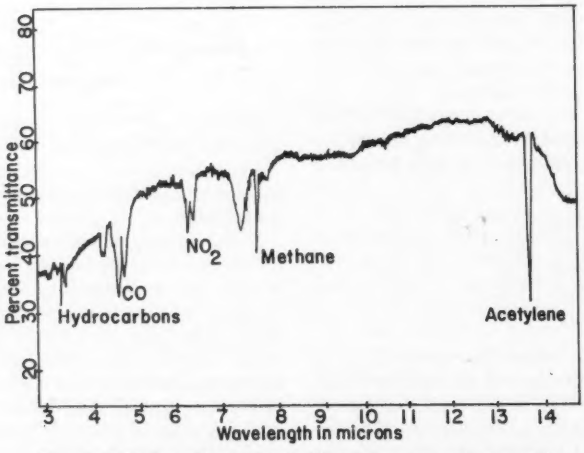

FIGURE 3. Boiler effluent (fuel oil) (ten-meter path gas cell).

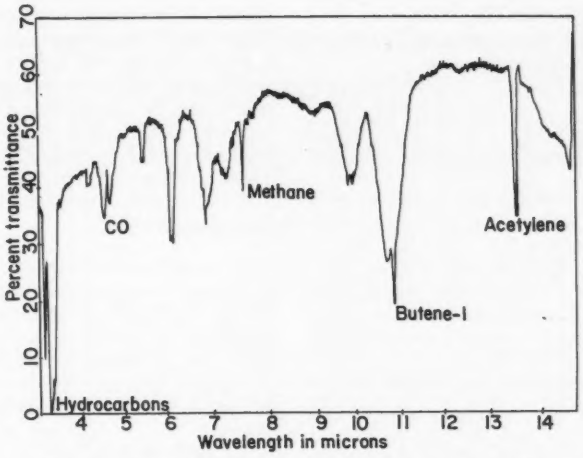

FIGURE 4. Standard gas mixture (ten-meter path gas cell).

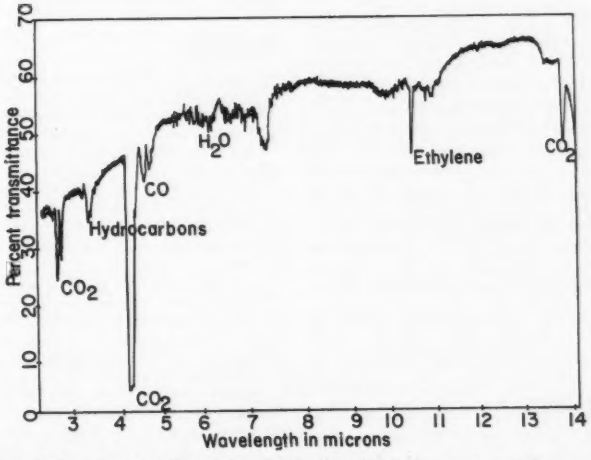

FIGURE 5. Incinerator effluent (multiple chamber) (ten-meter path gas cell).

As a result of these considerations it was felt that a closer indication of the quantity of low molecular weight hydrocarbons present in an unknown mixture would be obtained by measuring the concentration of methane, ethylene, butene-1, propylene and acetylene at their characteristic wavelengths and correcting for their contribution to the 3.4 micron peak by reference to Figure 1. At the same time, instead of using hexane as a standard of concentration for 3.4 micron absorbance, propane was chosen because it lies midway between ethane and butane in absorption intensity at 3.4 microns. Thus the term "other hydrocarbons as propane" represents the absorbance at 3.4 microns corrected for contributions made by methane, ethylene, butene-1, propylene and acetylene. For the low molecular weight hydrocarbons emitted from combustion and incineration sources, "other hydrocarbons as propane" ostensibly represents ethane, propane and butane.

Two problems associated with the collection and analysis procedure as described above were studied. The first of these concerned the possible change in concentration of collected effluents in the stainless steel tanks, and the second

TABLE III

Loss of Hydrocarbons on Standing and by Adsorption on Ascarite

Compound	Original concentration (ppm)	Concentration found after passing through ascarite (ppm)	Concentration found after 3 days residence in stainless steel tank (ppm)
Methane	50	48	48
Ethylene	50	47	48
Acetylene	25	23	24
Propane	75	75	73
Butene-1	50	46	47

TABLE IV

Some Results of Analyses on Combustion Effluents

Compound	Test No. 1	2	3A	3B	4A	4B	5	6	7	8
	Type of effluent*									
	SCI	SCI	MCI	MCI	MCI	MCI	MCI	MCI	BF	BG
	Afterburner									
	—	—	off	on	off	on	on	on	—	—
	Concentration (ppm)									
Methane	314	340	40	0	40	0	0	0	0	0
Acetylene	355	520	5	0	50	0	0	0	0	0
Ethylene	20	27	5	0	52	0	0	0	0	0
Other hydrocarbons†	60	75	5	0	85	0	0	0	13	4
Carbon monoxide	520	570	165		3900	150	10	10	0	10
Nitrogen dioxide	—	—	10	6	70	160	8	10	0	0
Nitrous oxide	—	—	—	—	—	40	75	100	0	0

* SCI—single chamber incinerator
MCI—multiple chamber incinerator
BF—Boiler—fuel oil
BG—Boiler—gas

† Corrected for the presence of methane, ethylene, acetylene, propylene, butene-1 and reported as propane.

concerned the possible loss of hydrocarbons in the process of transferring the effluent to the gas cell through an ascarite trap. Known mixtures in the tank and samples collected in the field were analyzed repeatedly over a three-day period. The results of these studies are shown in Table III and indicate that no appreciable loss of hydrocarbons takes place from either cause.

Analytical Results

Some typical analytical results are shown in Table IV. In addition to the hydrocarbons under discussion, the spectra of some combustion effluents show the presence of carbon monoxide, nitrogen dioxide and nitrous oxide. These are included in the table. No general conclusions concerning the significance of these results can be drawn until a sufficient number of tests have been made by the District's Source Test Crew. These tests are currently in progress.

Conclusions

In the infrared analysis of combustion effluents using a ten-meter gas cell, low molecular weight hydrocarbons are usually found. The concentration of these hydrocarbons are expressed as propane after correcting the absorbance at 3.4 microns for the contribution made by methane, ethylene, acetylene, propylene and butene-1. In the sampling method used it was found that changes in concentration did not occur on standing in stainless steel tanks, nor were there any appreciable losses on passing the samples through ascarite.

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Microdetermination of Ozone in Smog Mixtures: Nitrogen Dioxide Equivalent Method*

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Introduction

THE SPECIFIC microdetermination of low concentrations of ozone in air has been a very difficult, but important problem. The interpretation of the results of air pollution studies using iodometric methods is restricted because of their non-specificity. Thus the extremely low values found for ozone in the atmosphere of many cities may be suspected as erroneous because of the known negative interference of sulfur dioxide.[1] Furthermore it has been established that ozone is only a part of smog oxidant,[2, 3] and that the eye irritation and plant damage are not characteristic of ozone, but may be effects of the organic oxidants present in smog. Hence an understanding of basic smog chemistry requires convenient means for differentiating these mixtures into their oxidant components.

This report results from a study[4-6] dealing with the kinetics of synthetic smog oxidant generation by the reaction of ozone with 1-hexene. A major portion of the work was devoted to the development of analytical methods, since little progress could be made in the absence of a convenient, precise, and specific method for ozone. The success of the methods developed for this application suggests their use for a study of natural smog oxidants.

After a study of a considerable variety of iodide mixtures[5, 8] and organic reagents, it seemed unlikely that aqueous reagents could be developed that would be specific for ozone. This may be due to the very high oxidation potential and free radical nature of ozone, which favor many simultaneous reactions. The reactions could not be distinguished from those of oxidants such as hydrogen peroxide and organic hydroperoxides, since these liberate free hydroxyl radicals having a very high oxidation potential during the course of some of their aqueous reactions.[9] Furthermore, a negative interference from reducing pollutants such as sulfur dioxide could occur in the aqueous solutions, even though reaction did not occur in the gaseous state with ozone. Some non-aqueous ozone reagents were prepared, but were also found unsuccessful. A radically different approach thus seemed required for developing a specific method for ozone analysis.

Gas phase reactions appeared to have good theoretical possibilities. The availability of a well established method for nitrogen dioxide[10] suggested the use of either the ozone-nitric oxide or the ozone-nitrogen dioxide gas phase reactions for analytical purposes:

$$(1) \qquad O_3 + NO \rightarrow O_2 + NO_2$$

$$(2) \qquad O_3 + 2\ NO_2 \rightarrow O_2 + N_2O_5$$

The latter reaction is much too slow to be useful for low concentrations of ozone, although it was successfully used[4] for a gas phase titration at high concentrations in a dynamic flow system. This report deals with the application of Reaction 1 for the quantitative conversion (by excess nitric oxide) of ozone to nitrogen dioxide, in which form it was analytically determined. The validity of the procedure for pure ozone was demonstrated in a flowmeter system using a constant ultraviolet source, and by comparison with analyses using iodide reagents.

The method was made specific for ozone by using a controlled small excess of nitric oxide and the minimum flow reaction time which permitted the extremely rapid Reaction 1 to go substantially to completion. The secondary Reaction 2 was suppressed because its kinetic rate[11] is only 0.4% as fast as that of primary Reaction 1,[12] and because the primary reaction was favored by the higher concentration of nitric oxide. No other stable oxidants are known to be capable of converting nitric oxide to nitrogen dioxide in the short reaction time allowed. After appropriate blank corrections, a specific determination of ozone appeared to be accomplished even in the presence of other oxidizing or reducing pollutants.

A relatively simple and conveniently operated apparatus was developed to accomplish the ozone conversion to nitrogen dioxide. The determination is rapid and precise, and lends itself

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readily to automatic recording by minor adaptations of the systems now in use.[13]

Apparatus

A schematic diagram of the apparatus recommended for this procedure is given in Figure 1, and a photograph in Figure 2.

A small tank (1), containing a gas mixture of 1% nitric oxide in nitrogen, was fitted with a needle valve (2). In order to provide a smooth control over the working range of this valve (about 5° of rotation), the valve hand wheel was replaced by a three-inch lever moved by a screw against a similar lever clamped to the valve body. An appropriate stop was included to prevent excessive closing and damage to the needle or valve seat. Nitrogen dioxide impurity was removed by passing the gas through about 10 ml of 8-20 mesh Ascarite (sodium hydroxide on asbestos) between glass wool plugs in tube (7). A safety line (3) permitted abnormal excessive gas pressure to discharge through water bubbler (4) into waste bottle (5). Here the nitric oxide was oxidized by air (which was occasionally replenished) and the nitrogen dioxide was absorbed by Ascarite on the bottom of the bottle. The purified waste gas was discharged at a point remote from the sample air intake (10) through tubing connected at outlet (6).

The gas was metered at about 0.2 ml per minute through a tightly packed asbestos plug in three-way, T-shape, capillary stopcock (B). The plug consisted of acid washed, medium fiber asbestos (of the type used for Gooch crucibles) packed in one leg of the 1 mm bore in the stopcock plug. The pressure on the asbestos plug face was maintained constant by discharging the gas stream through the other leg of the bore through line (8) into water bubbler (4) (at a point one-half inch above the terminus of line (3), so that the latter did not ordinarily discharge gas). The metered gas was mixed in an atomizer arrangement (9) with the sample air stream entering at (10).

The gas mixer (9) was carefully designed (as a result of considerable experimentation) to minimize the otherwise serious nitrogen dioxide blank produced by the air oxidation of the nitric oxide stream. This reaction proceeds rapidly at high concentrations, but at a negligible rate at low concentrations, since it is kinetically third order. Diffusion of air into the capillary system was minimized by the high air velocity (about 1000 cm/sec) at the nozzle tip (about 1 mm diameter). Also, the high velocity of the air diluted the nitric oxide so rapidly that air oxidation was prevented. The inner capillary tube had an extremely fine bore (about 0.09 mm), drawn out from the capillary tubing of stopcock (B), which had a bore of 0.8 mm. This also provided a high gas velocity. The volume of the gas system from the stopcock to the nozzle tip was made minimal to reduce the accumulation of nitrogen dioxide during shutdown, since this gas was difficult to flush out and was quite likely adsorbed on the glass. Any air which diffused backwards through the asbestos plug during operation was flushed to waste line (8), which always carried a flow of at least 1 ml per minute.

The sample air-nitric oxide mixer (9) was connected at (11) with a minimal length of tygon tubing. (A later version, detail 9A, employs a ground joint which also permits cleaning of the 1 mm diameter orifice serving as the nozzle tip.) The gas entered tangentially and swirled down the neck of 200 ml reaction flask (12). By means of stopcock (C), the reacted mixture could be drawn at the rate of 0.4 liters per minute by vacuum source (18) through either sampling bubbler (13), or ballast bubbler (14) of equal resistance, then through trap (15), calibrated flowmeter (16), and needle valve (17).

The nitric oxide gas flows were calibrated versus the height of water in the bubbler by timing the motion of a drop of water in a one-ml graduated pipette in a horizontal position attached at (10). Stopcock (C) was closed (one-half turn from position shown in Figure 1). Initially (B) was closed (one-quarter turn counter clockwise from the position shown) and the system allowed to equilibrate so that the drop was stationary. Then stopcock (B) was opened to the position shown, and the motion of the drop past the graduations was timed. Bubbler (4) was a 250-ml graduated cylinder without a lip. A linear plot was obtained of flow rate versus the depth (volume reading) of water in the bubbler, from which the amount of water required for any desired flow rate could be determined. (If the air pressure in mixer (9) differs appreciably from atmospheric pressure in the system used, an allowance is made in the bubbler water depth so that the net pressure across the asbestos plug is that required from the calibration plot.) A few trials were necessary to determine the tightness of packing of the asbestos plug so that the desired 0.2 ml per minute flow was obtained with about eight inches of water pressure. This calibration was found to be sufficiently constant for the needs of the procedure. Care was taken never to wet the plug, since this necessitated its replacement and recalibration.

The nitric oxide system was constructed with heavy wall, small bore, glass tubing and butt-to-

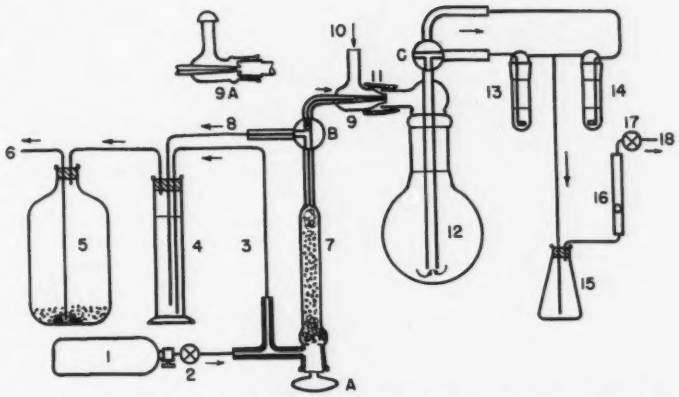

FIGURE 1. Apparatus for the determination of ozone by the nitrogen dioxide equivalent method: (1) Tank containing mixture of 1% nitric oxide in nitrogen. (2) Needle valve. (3) Safety waste gas line. (4) Waste gas bubbler. (5) Waste gas absorbing bottle containing air and Ascarite. (6) Waste gas vent. (7) Ascarite tube. (8) Waste gas line. (9) Gas-sample mixer. (9A) Detail showing revised gas-sample mixer permitting cleaning of orifice. (10) Sample air inlet. (11) Short tygon connection. (12) 200 ml reaction flask, with standard taper ground joint. (13) Sampling fritted glass bubbler. (14) Ballast fritted glass bubbler. (15) Trap. (16) Calibrated flowmeter. (17) Needle valve. (18) Vacuum source. (A) Stopper-stopcock for Ascarite tube. (B) Three way capillary stopcock with asbestos plug for metering gas. (C) Three way stopcock for sampling or bypass control.

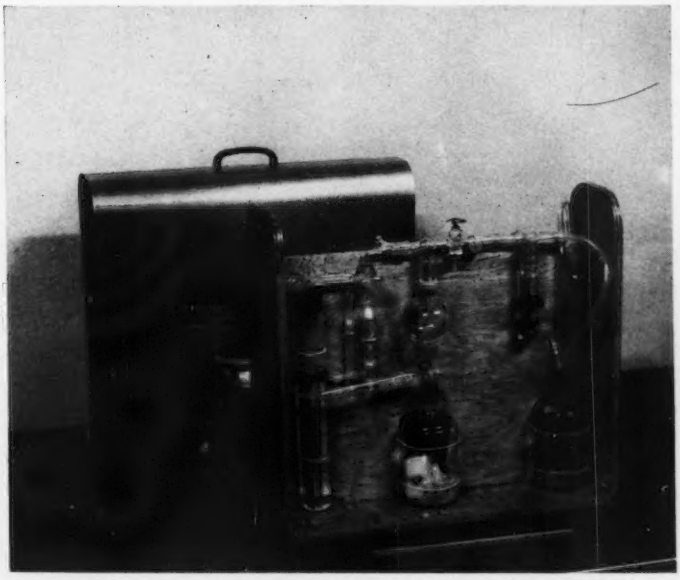

FIGURE 2. Portable model of the apparatus. Total weight with the carrying cover shown in the rear is 14 lbs. (excluding gas cylinder section which is detached and transported separately).

butt tygon connections lightly greased with fluorocarbon grease. The same grease was used for all stopcocks. The air was purged first through line (3), and then by opening stopcocks (A) and (B) through line (8), by a few hundred milliliters of tank gas. By leaving the tank permanently connected, further purging was unnecessary. Operations were conducted so that the bubbler (4) always indicated a positive pressure in the system and guaranteed that no air could enter.

Only ground glass joints and minimal lengths of greased tygon connections were used in the sample air system upstream from bubbler (13). This nitrogen dioxide absorbing bubbler had an outside tube with a capacity of about 60 ml and a 24/40 standard taper, female ground joint. The mating inner piece had a 9 mm diameter fritted disc with a maximum pore diameter of 60 microns to ensure efficient absorption, positioned close to the bottom of the absorber.

Recommended Procedure

Draw air through ballast bubbler (14) at the rate of 0.4 liter/min, by setting stopcock (C) one-quarter turn clockwise from the position shown. Open the tank valve, needle valve (2), then stopcocks (A) and (B) to the positions shown. The order given should be observed to ensure a positive pressure in the gas system at all times. Adjust needle valve (2) so that the bubble rate from line (8) indicates a gas flow of 1 to 5 ml per minute. (The initial calibration may be made with a 10-ml graduated pipette attached to the outlet of the bubbler, in the same way as previously described.) Allow fifteen minutes to flush out the residual nitrogen dioxide present in the mixing nozzle (9). Then turn stopcock (C) to the position shown and pass the sample through bubbler (13) containing ten milliliters of Griess-Saltzman reagent[10] for a timed interval. A ten minute sample should be adequate for most purposes. At the end of this time, turn stopcock (C) back to the ballast bubbler position. The ballast bubbler contains a 10 ml portion of water.

A blank nitrogen dioxide determination must then be made. Turn stopcock (B) one-quarter turn counterclockwise from the position shown, to shut off the nitric oxide flow, and flush the sample air system for five minutes. The same or a matched sample bubbler, containing another portion of reagent, is inserted into position (13). The nitrogen dioxide present in the air without addition of nitric oxide is then determined by sampling for the same period as above.

When shutting down for a prolonged period, first turn stopcock (B) to a position one-quarter turn clockwise from the position shown, then close stopcock (A), and finally close needle valve (2) and the tank valve.

Allow 15 minutes for the maximum red-violet colors to develop, and read within a few hours in a spectrophotometer at 550 millimicrons wavelength. The difference between the two determinations is taken as the concentration of ozone. A small correction (about 0.01 ppm) must also be deducted for the air oxidation of the added nitric oxide. This blank correction may be determined occasionally by sampling ozone-free air prepared by passage through a universal gas mask canister. It should be quite constant, and depends mostly upon the design of the apparatus.

Ozone Conversion Efficiency

The minimum theoretical efficiency for conversion of ozone to nitrogen dioxide may be calculated from the kinetic rate constant[12] of Reaction 1, 29 μatm^{-1} min^{-1} (at 25°C), by assuming the most inefficient condition of complete turbulence in the reaction volume from the point of mixing to the glass frit in the sampling bubbler. The amount of product produced per minute, Fn, is proportional to the volume of the reactor and the concentration of each reactant in the reactor, Equation 1. Because of complete turbulence the same concentrations also leave the reactor.

$$Fn = 29\ Vmx \tag{1}$$

Where F is the flow rate of the gas mixture, liters/min
n is the ppm of nitrogen dioxide produced by the reaction, as determined at the sampling bubbler
V is the total volume of the system for the gas reaction, liters
m is the ppm of excess nitric oxide in the reactor
x is the ppm of unconverted ozone in the reactor.

The conversion efficiency, E, is the ratio of the converted to the total ozone initially present:

$$E = \frac{n}{n + x} = \frac{1}{1 + x/n} \tag{2}$$

Introducing the value of x/n obtained from equation (1) we have the final result:

$$E = \frac{1}{1 + F/(29\ Vm)} \tag{3}$$

The value of V/F has been called flow reaction time in this report. This is about ⅔ minute in the apparatus recommended, from which we can calculate that for an excess, m, of one ppm, the conversion efficiency, E, is 95%; if the excess is 4 ppm E is 99%. In the kinetic study a flow reaction time V/F of 0.073 minutes (about 4 seconds) was used; for this condition, a 10 ppm excess was required to yield 95% conversion efficiency.

An experimental study to verify these theoretical calculations was conducted by metering into the sample air stream varying amounts of ozone from a constant and pure source. The source consisted of a 4 watt ozone-producing ultraviolet bulb in a two liter brown bottle, through which one liter of air per minute was passed. All air was purified by scrubbing with dichromate-concentrated sulfuric acid, followed by Ascarite, and/or by passage through a universal gas mask canister.

Comparative analyses were also made using a midget impinger containing 10 ml of 1% potassium iodide neutral buffered (0.1M KH_2PO_4, 0.1M Na_2HPO_4) reagent for collecting samples almost simultaneously. This reagent has been shown[4, 8] to yield stable and precise results using manual sampling techniques. Forty-five minutes were allowed for complete iodine liberation, and the color read in a spectrophotometer at 352 millimicrons.

Figure 3 shows the experimental results obtained with 5 ppm added nitric oxide and about 40 seconds flow reaction time. In Run 210 two minute samples were collected, and in Run 211 five-minute samples were collected. A good linear relationship was found between the nitrogen dioxide analyses and the ozone flowmeter readings.

The iodine results, given in the same figure, show two lines displaced downwards but parallel to the nitrogen dioxide line. It was determined that the displacement was caused by a fixed loss of iodine on the glass surfaces of the impingers from all the samples. Equal losses occurred from the longer samples, but the percentage error was less because the colors were darker. The same losses could be observed by pouring measured weak iodine colors into clean dry impingers, regardless of careful cleaning of the glass surfaces with dichromate-concentrated sulfuric acid and by various other means. Traces of laboratory dust were found to cause even greater losses. These effects are in agreement with the phenomena reported by Wolfenden.[14] Considering the widely differing nature of the two methods, the agreement was excellent.

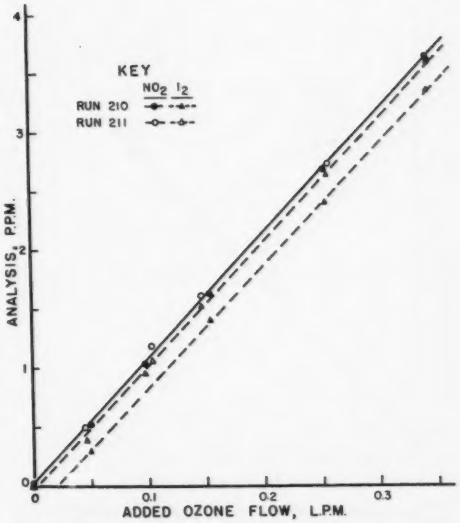

FIGURE 3. Analyses of pure ozone by two methods, compared with flowmeter values. Circles represent analyses by nitrogen dioxide equivalent method, using 40 second flow reaction time and 5 ppm added nitric oxide. Triangles represent almost simultaneous analyses using 1% potassium iodide neutral phosphate buffered reagent. Sampling times were about two minutes in Run 210 and 5 minutes in Run 211.

Figure 4 shows the experimental relationship between the two methods when much higher concentrations of nitric oxide were added and a four second flow reaction time was employed for the conversion. These extensive data are from the kinetic study.[5, 7] 1-Hexene was present in these mixtures in amounts from 1.4 to 36 ppm, but had no adverse effect on either method. The age of the mixtures was only about four seconds, and no appreciable reaction had occurred between the ozone and the hexene. (Different results were obtained for the same mixtures after aging, as will be discussed below.) At low ozone concentrations Figure 4 shows iodine results which are about 0.1 ppm low compared to both the nitrogen dioxide values and the flowmeter values.[5, 8] In the range 20 to 80 ppm of ozone the nitrogen dioxide values became progressively low, whereas the iodine values agreed well with the flowmeter values. This loss of conversion efficiency is not understood, since ample excess nitric oxide was added. However, the agreement between the two methods was excellent over a very wide range, and the validity of the nitrogen dioxide method was established be-

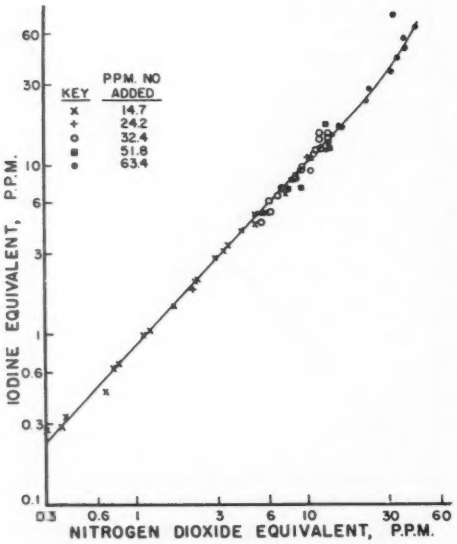

FIGURE 4. Comparison of results by two methods applied to unaged ozone mixtures with 1-hexene. Flow reaction time of four seconds was used for nitrogen dioxide equivalent method. Concentration of 1-hexene varied from 1 to 37 ppm.

low 20 ppm of ozone, which is the range of practical interest.

Effects of Interfering Gases

The effects of hydrogen sulfide and sulfur dioxide were determined by metering them into the ozone stream using motor driven glass syringes filled from tanks. Analyses were conducted at the same ozone concentration both with and without the added interference. The age of the mixtures was so short (four seconds) that no appreciable reaction appeared to occur between the gases at the low concentrations used. The interfering effects observed were small even when the concentrations of hydrogen sulfide and sulfur dioxide were far above any level occurring in the atmosphere. Table I shows the results for 5 ppm added nitric oxide and about 40 seconds flow reaction time for the conversion. Similar results were obtained for 15 ppm added nitric oxide and four seconds conversion time. Sulfur dioxide in tenfold to hundredfold ratio to ozone caused results about 7% low, if the colors were read when 15 minutes old. The fading rate was increased, so that an equal additional loss occurred if reading was delayed another hour. These losses probably could be reduced by adding 1% acetone to the sampling reagent as described by Saltzman.[10] The effect of like amounts of hydrogen sulfide was found to be negligible, both on the amount of color obtained and on the fading rate.

The interference of hydrogen sulfide and sulfur dioxide with the iodide method was also determined at the same time, and found to be very serious, since no test at all for ozone was the result in all cases. Thus in polluted air containing these substances, the two methods would be expected to give widely differing results for ozone.

The interference of the synthetic smog oxidants produced by the ozone reaction with 1-hexene was determined by mathematical analysis of the kinetic data. Figure 4 has presented the agreement between the two analytical methods for the fresh unreacted ozone-1-hexene mixtures. After 20 to 34 minutes of flow reaction time in completely turbulent passage through a glass bottle, the same mixtures yielded diverging results by the two methods, the iodine values always being higher. These data could be explained by hypothesizing that a portion of the reaction products was oxidants which continued to give the iodine test, but did not give the nitrogen dioxide test. This hypothesis is supported by the plot in Figure 5. The ordinate, which is the difference between the two analytical results, termed "synthetic smog oxidants", was found to be 17 to 25% of the ozone consumed in the reactor (difference between entering analysis and exiting analysis by nitrogen dioxide equivalent method), over a hundredfold range. Furthermore, the nitrogen dioxide analyses portrayed a simple kinetic pattern of the reaction, first order with respect to each reactant, whereas the pattern shown by the iodine data could not

TABLE I

The Effect of the Presence of Interfering Gases

Interfering gas added	Analysis, ppm	
	Pure ozone	Mixture
28 ppm H_2S	0.43	0.43
" "	1.04	1.02
" "	1.47	1.48
" "	2.47	2.44
" "	3.26	3.26
32 ppm SO_2	0.39	0.37
" "	1.35	1.30
" "	2.31	2.48
" "	3.78	3.58

be interpreted. However, if the iodine results were corrected on the basis of the above hypothesis, the identical simple kinetic pattern was obtained as for the nitrogen dioxide results. From this evidence it was concluded[5, 7] that the organic oxidants did not interfere with the nitrogen dioxide equivalent method for ozone.

From a theoretical viewpoint, it seems likely that under appropriate conditions free radicals should give the nitrogen dioxide equivalent test. Consideration[5, 6] of the balance of nitrogen oxides in smog forming processes suggests that free radicals may play an important role in catalyzing the air oxidation of nitric oxide. Free radicals are produced by the reaction of organic pollutants with ozone. Hence the smog-forming potential of organic substances should be closely related to their ability to catalyze this oxidation in the presence of ozone. Such an effect was sought but not found in the kinetic study. Apparently the high concentrations and the large excess of nitric oxide used were unfavorable conditions. Perhaps surface reactions are involved. This possibility appears worthy of further investigation under more natural conditions.

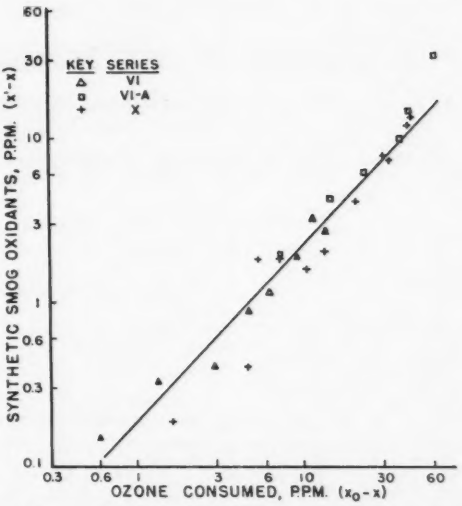

FIGURE 5. Interpretation of the differences in results by two methods applied to partially reacted ozone mixtures with 1-hexene. Here x' represents iodine equivalent, and x the nitrogen dioxide equivalent of the reacted mixture; x_0 represents the ozone present in the mixture before reaction. The ordinate, representing reaction products which give the iodine but not the nitrogen dioxide test, is 17 to 25% of the ozone consumed by the reaction over a hundredfold concentration range.

Summary

A new method has been presented for conveniently and specifically determining low concentrations of ozone in polluted air, even in the presence of large amounts of other commonly occurring oxidizing or reducing gases. Ozone was stoichiometrically converted to (and determined as) nitrogen dioxide, by addition of controlled amounts of gaseous nitric oxide to the sample air stream and allowing a short reaction flow time. Better than 95% conversion was obtained in a convenient apparatus which was developed, when one ppm excess nitric oxide and forty seconds reaction time were used. In the short time allowed, oxidation of nitric oxide by air and organic oxidants was negligible. Results for pure ozone were in good agreement with those of an iodide reagent. For synthetic smog oxidant mixtures (generated by the ozone reaction with 1-hexene) the method appeared specific for ozone, whereas the iodide reagent also responded to organic oxidants. (Thus the mixture could be differentiated into two oxidant components by simultaneous application of the two methods.) Reducing gases such as sulfur dioxide and hydrogen sulfide did not appreciably interfere even in one hundred to one ratio to ozone. The method should make possible interesting new data for polluted air. It should be readily adaptable to automatic recording of ozone in smog without interference from associated pollutants.

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An Appraisal of an Industrial Air Contaminant by Electrochromatography*

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THIS PAPER describes the use of a combination of laboratory techniques to study an industrial air pollution problem. The problem occurred in an industrial plant which used thallium salts as concentrated solutions in its processes for heavy medium separations. At one period, several employees had medical complaints indicative of thallium intoxication. These complaints occurred despite presumed precautionary measures, including low heating temperatures, thorough washing of thallium containing residuals, washing of hands before eating or smoking and careful plant housekeeping to prevent the accumulation of dusts. A preliminary survey of the plant was made by members of the staff of the Graduate School of Public Health of the University of Pittsburgh. Initial recommendations included the installation of a fume hood, substitution of wet mopping for sweeping and dusting and a program of air analysis to determine the sources of thallium contamination.

To locate the source of thallium contamination, analysis of the air at the time of the various plant operations was required. It was decided to analyze the particulate matter in the air for thallium content. Standard procedures for the collection, separation of thallium from other metallic contaminants and analysis appeared to be time consuming and uncertain. To overcome these difficulties, a combination of techniques was utilized. The air samples were collected as spots on paper tapes by means of the Automatic Smoke Sampler while compiling simultaneously a log of plant operations. The sampler tapes were then subjected to paper strip electrophoresis for separation and identification of thallium. This combination of techniques was effective, when correlated with plant operations, in demonstrating the location of air contamination by particulates containing thallium.

* The work reported in this paper was done under National Institutes of Health Grant RG-4924, Application of Electrochromatography to Analytical Problems in Industrial Hygiene and Air Pollution.

Collection Procedure

The Automatic Smoke Sampler (Figure 1) is available from the Research Appliance Company of Allison Park, Pennsylvania and has been used in many air pollution studies. It may be regulated for collection of samples at varied time intervals and varied space intervals on the sampling tape. The sampling time was adjusted for one hour and the space interval was set at twelve inches to allow the paper strip to be used in the electrophoresis procedure. A roll of sampling tape (Whatman #4 filter paper) will take about 96 samples when set for twelve inch intervals. The tape can be run for four complete days, showing air conditions both during working hours and those periods when the plant is idle. During these sampling periods a running record of types of operations in progress and their time span was kept. The tapes were marked with the record of the time at several intervals during the working day to afford the laboratory a check with the operations log. The sampler was located on a bench in a corner of the small room in which all thallium operations took place.

Analytical Procedure

Preliminary experiments were performed to determine the conditions necessary to separate thallium quantitatively from the other contaminants by paper strip electrophoresis. Figure 2 shows the type of electrophoresis cabinet used in this work. The instrument is obtainable from Arthur H. Thomas Company of Philadelphia. The sampling tapes, after exposure, were returned to the laboratory and were cut at twelve inch intervals, with the center of the dust spot four inches from the end of the strip. The strips were subjected to electrophoresis under the following standard conditions previously determined as optimum.

Paper Strips: 1½ inches wide and 12 inches long, Whatman #4

Start line: center of dust spot four inches from the anode end of the strip

Buffer: 0.1*M* solution of sodium borate and boric acid, pH 8.7 (11.44 grams sodium borate and 4.33 grams boric acid made up to a liter with distilled water)

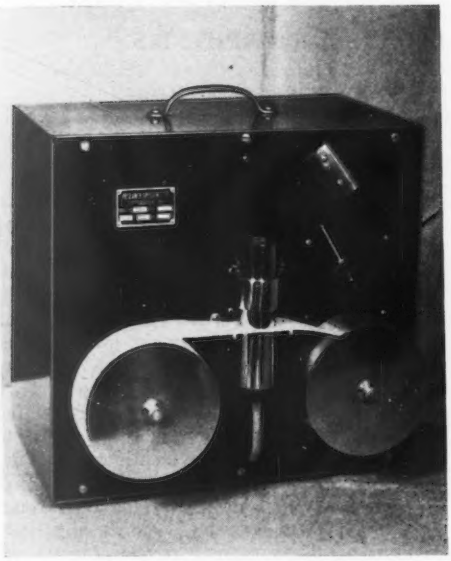

FIGURE 1. Automatic smoke sampler.

Voltage: 200 volts dc
Sample running time: 60 minutes
Conditioning time: none

Sample strips were individually dipped in buffer and, without blotting, were attached to the support rack of the instrument. The current was applied and, at the end of an hour, the rack was removed and the strips, still attached to the rack were dried in gentle (about 40°C) heat. After the strips were dry, they were sprayed with a one per cent solution of sodium sulfide. The intensity of brown color was proportional to the quantity of thallium present. Known amounts of thallium, 1, 3, 5, 10, and 25 micrograms, were electrophoresed under standard conditions and their color developed with one per cent sodium sulfide solution. These were used for visual and memorized comparisons in estimating the quantity of thallium present in the plant samples. These estimations of quantity must be made quickly after color development because of the oxidation of the brown sulfide of thallium to the white sulfate. The standards demonstrated that as little as one microgram of thallium may be detected visually by this technique.

Some laboratory tests were run on the industrial thallium solution used in plant processes to study the mechanism of thallium transmittal to the air during concentration of the thallium solution. The solution was heated in a flask fitted with a thermometer in the solution, a spray trap

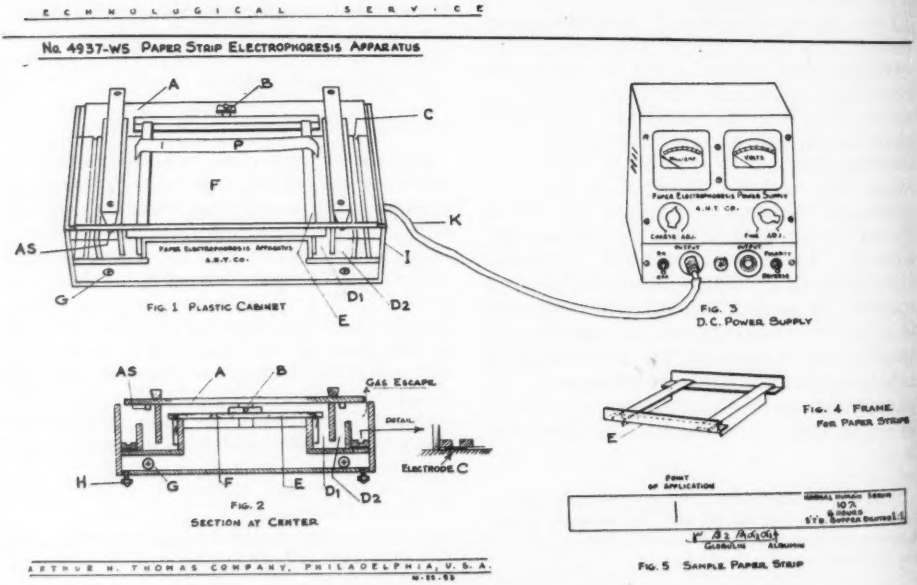

FIGURE 2. Electrophoresis apparatus.

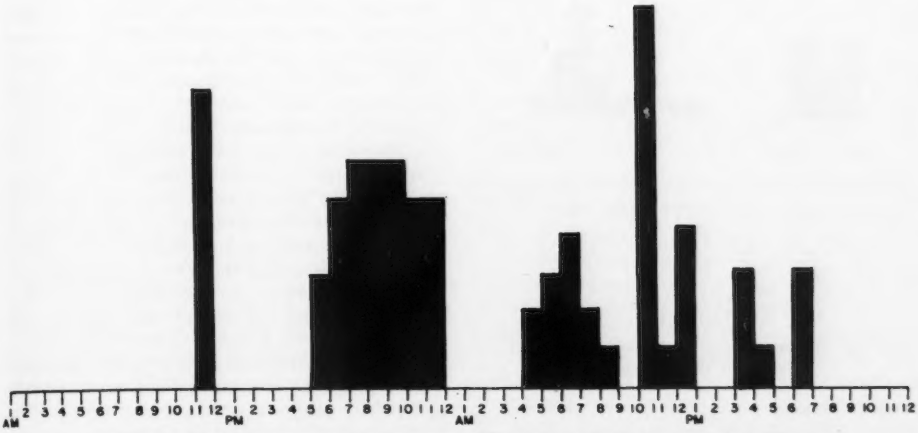

FIGURE 3. Thallium content of hourly atmospheric samples before control measures.

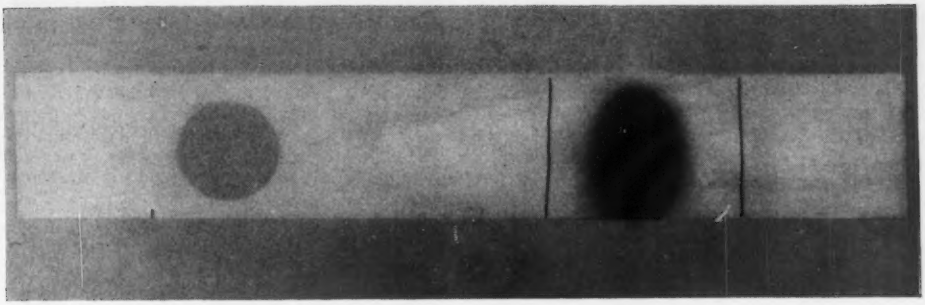

FIGURE 4. Paper strip after electrophoresis, showing original circular dust spot on left and migrated oval heavy thallium spot on right.

and a condenser. By testing distillates coming over at various temperatures with sodium sulfide solution, it was demonstrated that thallium is present in the distillate at temperatures as low as 116°C in the thallium solution. When nitrogen was used to sweep the vapor in the system into a collector containing sodium sulfide solution, colorimetric evidence of thallium was found when the solution temperature was 100°C and that of the vapor 65°C. This carry-over increased markedly with elevation of temperatures. The black precipitate formed was subjected to emission spectroscopy and was found to contain thallium as the major constituent with traces of elements derived from the glass frit on which the precipitate had been collected.

Results

A comparison was made of the thallium concentration found and the plant operation in progress at the time. Figure 3 illustrates the variation of thallium concentration with time. Reference to the work log showed that there was no thallium present in the air when the plant was not in operation and that there was a wide variation of contamination intensity during working hours. High concentration peaks during centrifugation and screening of residual solids and during concentration of thallium solutions implicated these operations as sources of air pollution. The highest thallium concentration was observed when the prescribed maximum temperature for concentrating solutions was exceeded. The paper strip for this analysis is shown on Figure 4. This spot is estimated to be about one milligram of thallium.

Air contamination during centrifuging and screening of residuals which had been in contact with the thallium solution showed that washing operations were not as complete as was supposed.

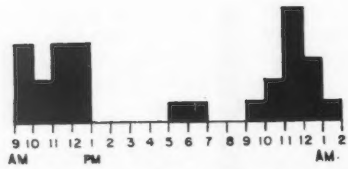

FIGURE 5. Thallium content of hourly atmospheric samples after control measures were instituted.

TABLE I

Typical Log of Operations before Control Measures Were Started

Time	Reaction	
1 AM	0	
2	0	
3	0	
4	0	
5	0	
6	0	
7	0	
8	0	Still turned on
9	0	
10	0	Screening
11	+++++++	Screening
1 PM	0	
2	0	
3	0	Added thallium solution to still
4	0	Added thallium solution to still
5	+++	Still left open with fire on
6	++++	Centrifuging
7	+++++	
8	+++++	Emptied still and began recharging
9	+++++	
10	++++	
11	++++	Swept floor
12	0	
1 AM	0	
2	0	
3	0	
4	++	Opened window. Lit still.
5	+++	
6	++++	Screened
7	++	Drained still, cooled in sink
8	+	Charged still and lit.
9	0	Drained still, recharged and lit
10	++++++++++	Added solution to still
11	+	Screened
12	++++	Added to still. Screened
1 PM	0	Drained still and recharged
2	0	
3	+++	Centrifuged
4	+	
5	0	
6	++++	Swept floor
7	0	
8	0	
9	0	
10	0	
11	0	
12	0	

This was further proved by leaching out some especially well washed residual with dilute acetic acid and determining the thallium gravimetrically as the chromate. The amount of contaminant found in this residue, (0.2%), pointed clearly to a source of air pollution since these residuals were centrifuged and screened in the open.

As a result of these findings, it was recommended that all concentrating operations and cooling of the hot solutions be done in a hood, with careful temperature control, that screen covers be used during the screening process, that floors and tables be wet mopped and that dust scattering during handling of solid thallium and thallium salts be avoided. After these recommendations had been incorporated into the operations program, the atmosphere was sampled again. The results are shown in Figure 5. The findings indicated on this graph are on the same scale as those in Figure 3. This improvement in plant conditions, while not reaching the ultimate, was accomplished by recognition of the specific sources of contamination.

Discussion

The choice of the two techniques for evaluating particulate air contamination arose from work done previously in this department in separating several metal contaminants in dust samples collected from the air in the Pittsburgh area, by means of the Automatic Smoke Sampler. The efficiency of the Sampler for the collection of particulates was of primary importance. Inquiry elicited the information that the paper tape (Whatman #4) had been evaluated and is one hundred per cent effective for particles of five microns or more and is about one third that efficiency for particles as small as one fourth micron. These dust spots from the Pittsburgh atmosphere were subjected to electrophoresis under operating conditions suitable for the contaminants which were anticipated in such a sample. Lead and iron were electrophoretically separated from the spots and chemically detected.

The selection of operating conditions, especially that of buffer composition, is closely related to the chemical behavior of the ion in question. For instance, lead and thallium can be effectively separated by use of a borate buffer due to the solubility of thallium borate which moves ionophoretically on the paper strip, and the relative insolubility of lead borate, which remains at the point of application of the sample. Judicious use of such properties of an element can, in many cases, solve separation problems which seem difficult.

Within the limited scope of the work we have

done in ionophoresis, including mainly lead, mercury, boron and thallium, there has appeared a factor which may become useful as a method of ion identification. The preciseness of the distance travelled by each of the elements mentioned under a controlled set of conditions is such that, without detection measures these areas may be cut from an ionophoresed strip and used in ordinary chemical elution and determination. Further work in this field could prove that this distance of travel alone may serve as a method of detection and identification.

Another observation of some significance is that, even in the case of the heaviest thallium contamination encountered in this series, the removal of thallium from the dust spot was complete, because when the whole strip was sprayed with sulfide solution, there was no evidence of any of the contaminant remaining in the dust spot, nor in process of moving toward the migration line. It can therefore be assumed that the ionophoresis to the migration line is quantitative.

The increasing use of thallium in industry, coupled with its toxicity, points to the necessity for further study of the mechanism of its transmittal to the atmosphere. The limited investigation, conducted in connection with this paper, produced results which are sufficiently significant to industrial hygiene to warrant a more comprehensive program of research.

Sodium sulfide solution, while non-specific, was used in the series of evaluations to develop color for the estimation of thallium. The more specific detectors of thallium are either not useful on paper strips or are useful only on the trivalent ion of the metal. The paper strip used in this method does not lend itself to the strong oxidation procedure necessary for conversion of the thallous ion to the thallic one. The sulfide solution allowed estimations of as little as one microgram of the contaminant without the possible danger of losses in the oxidation process. The use of densitometric measurements of color intensities in this technique is contemplated when a method for controlling sulfide oxidation is perfected.

Summary

In an industrial plant using thallium in its processes, several employees showed signs of thallium poisoning and were hospitalized. To evaluate the sources of contamination, dust spots, collected by the Automatic Smoke Sampler at hourly intervals, were subjected to electrochromatography. The migrated thallium was sprayed with a solution of sodium sulfide to develop color. By comparison with standard amounts of thallium, treated in the same way, estimates of the severity of contamination were made. A log of plant operations and their timing was correlated with the electrochromatographic findings and the processes involved in the contamination were implicated. When recommendations, designed to correct some of the causes of contamination were incorporated into plant operation, a marked improvement in hygienic conditions resulted.

It is anticipated that this combination of techniques, air sampling on paper tapes and electrochromatography of the strips containing the particulate matter of the contaminants, may be found useful, under suitable operating conditions, for the evaluation of other air contamination problems. This technique could also be useful for pollutants other than particulate matter if the collecting strips are suitably selected and prepared.

Determination of Decaborane with Dipyridyl Ethylene*

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THE BORON hydrides have become of increasing importance as both military and industrial chemicals. Three of these boron-hydrogen chemicals, namely, diborane, pentaborane and decaborane, have been used extensively and are included in the American Conference of Governmental Industrial Hygienists' list of threshold limit values.[1] This paper deals with the chemical analysis for decaborane.

Decaborane has, in addition to its military uses, been proposed as a catalyst, vulcanizer and mild reducing agent.[2] In addition to its many unique properties, it is also highly toxic. The toxicological properties and health hazards of decaborane have been reviewed by Rozendaal,[3] Krackow,[4] Lowe and Freeman,[5] and Roush.[6] The 1958 value for a threshold limit for decaborane has been set at 0.05 ppm.[1]

The molecular weight of decaborane ($B_{10}H_{14}$) is 122.31. The crystals are white, rhombic needles having a melting point of 99.7°C and a density of 0.94 g/cc at 20°C. The vapor pressure is very low, being about 0.05 mm Hg at 25°C. Decaborane is insoluble in water but is generally soluble in organic solvents, including alcohol, ether and xylene. Hydrolysis is very slow at room temperature, reportedly less than ten per cent in ten days.[2]

The boranes have often been compared by analogy to the carbon-hydrogen molecules in the alkane series. However, the common valence theories used in defining the structure of alkanes cannot be applied to the boranes. The structure of decaborane crystals has been determined by x-ray diffraction and is in agreement with the available electron diffraction data.[7] This structure has been referred to as the "basket" or "open clamshell". The boron atoms are at ten of the vertices of a somewhat distorted regular icosahedron. Each of ten hydrogen atoms is attached to a single boron atom. However, the remaining four each bridge two boron atoms to form the distinctive boron-hydrogen-boron bonding system.

A review of the literature on the chemical analysis of decaborane indicates the use of a variety of principles. One general technique involves the hydrolysis or digestion of the decaborane molecule to boric acid or borates. The borates are then determined by acid-base titration[8] or by colorimetric measurement with such chemicals as turmeric,[9, 10] quinalizarin,[11] carmine,[12, 13] 1,1′-dianthrimide,[14] or diaminochrysazin.[15] W. H. Hill and co-workers have reported the measurement of decaborane in alkaline solutions by ultraviolet absorption[16] and by the reduction of phosphomolybdic acid.[17] Another method utilizing the reducing power of decaborane employed by W. H. Hill is the reduction of triphenyltetrazolium chloride to form the red-colored formazan.[18] This reagent has been the basis for the development of instruments to monitor contaminated atmospheres.[19] One of the first analytical methods for decaborane was the silver nitrate reagent reported by Etherington and McCarty[20] for detection with a monitoring device.

At least two methods have been presented which are based on the reaction of boranes with nitrogen. D. L. Hill, Gipson and Heacock[21] reported a method for the direct determination of decaborane based upon the formation of an orange-red solution with N,N-diethylnicotinamide. This method is reported to be applicable in aqueous solutions as well as in cyclohexane. W. H. Hill and Johnston[16] investigated a large number of nitrogenous compounds and found that decaborane combines with quinoline to form a red compound which lends itself to colorimetric analysis. This reaction is reportedly best carried out in an aromatic solvent, as it does not occur in alcoholic media or in water.

As with many analytical procedures, the problems associated with the determination of decaborane are specificity, sensitivity, simplicity of technique and collection of samples. The method described in this paper is completely analagous to the quinoline method with the principle advantage of increased sensitivity. The reagent used is 1,2-bis(4-pyridyl)-ethylene and will be referred to as PE. (Available as purified crystals from the Aldrich Chemical Company, Inc., 2369

* Presented at the Industrial Health Conference, Chicago, Ill., May 1, 1959. This investigation was supported in part by the Callery Chemical Company under a contract from the Bureau of Aeronautics, Department of the Navy.

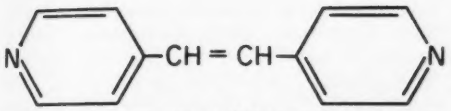

FIGURE 1. Structure of 1,2-bis(4-pyridyl)-ethylene.

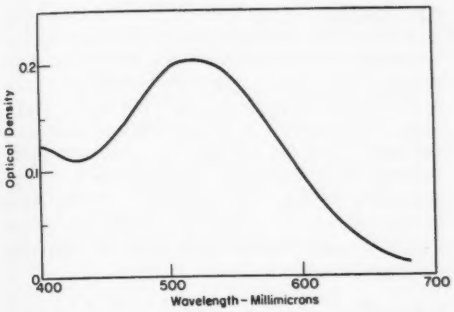

FIGURE 2. Absorption curve for decaborane-PE color complex, made with Universal Coleman Spectrophotometer Model No. 14.

N. 29th Street, Milwaukee 10, Wisconsin.) The structure is seen in Figure 1.

Procedure

The reagent is prepared by dissolving 0.5 gram of PE in 100 ml of xylene. The PE reagent is added to decaborane in xylene and forms a clear pink to red solution. The colored solution shows an absorption peak at 515 millimicrons wavelength as seen in Figure 2. At room temperature the color development reaches maximum intensity within thirty minutes. Figure 3 illustrates this color development with time for several different concentrations of decaborane. The maximum color has been found to be stable for at least one hour and then fades slowly.

The standardization curve has been obtained with resublimed decaborane freshly dissolved in commercial C. P. xylene. Five milliliters of the PE reagent were added to five milliliter quantities of different concentrations of decaborane in xylene. After thirty minutes the optical density was measured in a Universal Coleman Spectrophotometer Model No. 14 at 515 millimicrons wavelength. Throughout all experiments the total volume of solution used was ten milliliters in a nineteen millimeter glass cuvette. Concentrations of decaborane are expressed as micrograms of boron per milliliter as referred to the final volume of ten milliliters. The PE reagent was used as a blank for zero settings. Figure 4 shows a typical calibration graph. A comparison would show that the PE method is about twice as sensitive as the quinoline method.

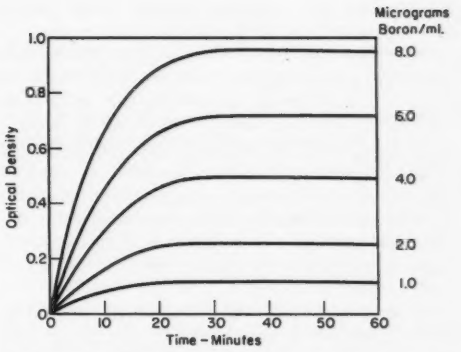

FIGURE 3. Color development of varying concentrations of decaborane-PE color complex with time.

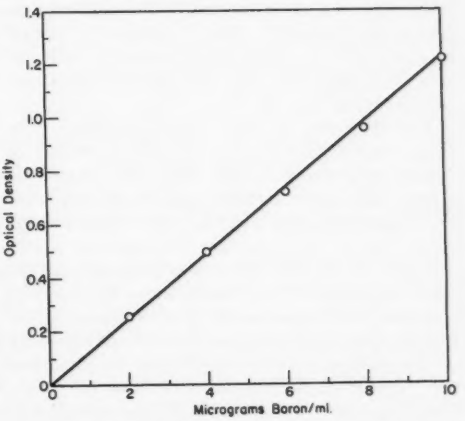

FIGURE 4. Standard calibration curve for decaborane-PE color complex.

Discussion

A variety of factors relating to this method have been noted and investigated. The concentration of PE reagent was varied from about 0.06 per cent to about 1.0 per cent (approximately saturated). The 0.5 per cent solution was found to be best suited.

The principle advantages of the PE reagent over quinoline appear to be increased sensitivity, more rapid color development and lower reagent blank readings. It has already been mentioned that the sensitivity of color development is approximately doubled. The maximum color development is reached within thirty minutes whereas the quinoline method requires ninety minutes. The PE reagent blank is considerably

lower than the quinoline reagent blank unless the quinoline is freshly distilled.

The color developed with PE reagent has been found to fade only slowly. However it has been noted that after several hours, the more concentrated solutions have a tendency to form a red precipitate. It has also been noted that if the color developed is too intense to be read in the spectrophotometer, simple dilution with xylene or PE reagent will give erroneous results. In such cases it is necessary to dilute the unknown solution with xylene prior to color development.

Several solvents have been investigated as substitutes for xylene. Acetone, chloroform and carbon tetrachloride showed some possibilities but were not considered more advantageous than xylene.

Specificity of PE reagent is apparently similar to that of the quinoline method. Pentaborane in xylene gave an immediate color with PE reagent which faded rapidly. This is similar to results reported with quinoline. Diborane reportedly reacts with quinoline but does not develop significant color.[16]

Extensive air analyses have not been performed with PE reagent. Limited experiments, again similar to quinoline, indicate that the PE reagent in a gas bubbler collecting bottle efficiently absorbs decaborane from the air current.

There have been no efforts to establish the exact nature of the color complex. W. H. Hill[16] indicated that decaborane and quinoline combine in a ratio of one to one. D. L. Hill[21] reported on the basis of infrared absorption spectra that the N,N-diethylnicotinamide-decaborane reaction occurred at the boron-hydrogen-boron bridge structure of the decaborane molecule.

The boron-nitrogen bond has often been compared with the carbon-carbon bond. Boron is a little smaller than carbon and nitrogen is a little larger. The boron atom can share the two electrons of the nitrogen atom in a coordinated linkage. It has been shown that the stability and rate of formation of the boron-nitrogen bond may be markedly affected by steric hindrance from different groups[22] attached to the boron and nitrogen molecules. This is in agreement with Hill's[16] finding that decaborane did not produce a color when a methyl or hydroxyl group was attached to the carbon adjacent to the nitrogen in the quinoline molecule.

The development of this method illustrates an important factor in selecting reagents for colorimetric analysis. The early theories correlated color with structural features according to the concept of chromophores and auxochromes as color producing or enhancing features. Reinterpretation and extension of these theories in terms of current electronic theory[23] recognize these structures according to their ability to accept or donate electrons. Certain structure changes involve electron transitions which may shift absorption of light to visible wavelengths. The intensity of color seems to be related to the resonance of the structure. Thus a conjugated system allowing resonance may enhance the color. It appears that the number of resonance structures possible and the possibility of the extension of conjugation to increase the separation of charges are the important factors. This apparently explains the increased sensitivity of PE over quinoline. On the basis of these theories it should be possible to design molecules and predict their relative merit for colorimetric analysis.

Summary

A new reagent, 1,2-bis(4-pyridyl)-ethylene, is proposed for the determination of decaborane in xylene solution or in air. This reagent is suggested for those applications of the quinoline method in which an increased sensitivity is desired. Some factors relating to the use of the method have been discussed. It is further suggested that the use of electronic theories of color may lead to the discovery of molecules providing an even greater sensitivity of detection.

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SYMPOSIUM ON CONTROLLING DISABILITY

A NATIONAL SYMPOSIUM on the problem of controlling disability, especially in the areas of cardiac disease, the degenerative diseases, and physiologic disorders, was sponsored by the Liberty Mutual Insurance Company in Boston, October 15 and 16, 1959. The symposium consisted of panel discussions devoted to three of the most common and urgent problems in disability control and also of a series of prepared addresses by leaders from industry, labor, medicine, government, law and insurance.

One of the highlights of the symposium was the session devoted to the implications of the lastest molecular research at it relates to the connective tissues and the degenerative diseases of the aging. The important insights and findings of the symposium were recapitulated by Dr. Rene Dubos of the Rockefeller Institute.

Hemoglobin Analysis for Aromatic Nitro and Amino Compound Exposure Control

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THE ASSOCIATION of chemical cyanosis with the manufacture of aromatic nitro and amino compounds has been a well-known occupational hazard almost from the first commercial production of nitrobenzene and aniline. Although the human biochemical reactions were not understood, reduced oxygen carrying capacity of the blood producing general tissue anoxia after absorption of these fat soluble aromatic compounds was recognized very early in the history of the dye industry.[1]

Although the cyanosis producing potential of nitrobenzene and aniline are both profoundly altered by the character, number and position of substituents in the benzene ring, physiological action is not well documented. Contact with the substitution products has shown that dinitrobenzene, nitroanilines, chloronitrobenzenes and the chloroanilines possess considerably greater cyanosis potentials than would be expected from the activity of the parent compounds. Recent experience has established the chloroanilines as particularly effective cyanosis producing agents. Excessive exposure without prompt and adequate medical attention can be fatal. However, the adverse physiological activities have been brought under control by good manufacturing procedures, medical guidance and industrial hygiene collaboration.

The reaction products of hemoglobin (Hb) with metabolites of the aromatic nitro and amino compounds have been rather loosely classified in the past as "methemoglobin" from similarity of the blood absorption spectra to complexes in which the iron has been oxidized to the ferric valence state.[2] Only recently work with radioactive labeled aniline derivatives disclosed the complex nature of these hemoglobin and methemoglobin derivatives which are in dynamic equilibrium during the development and recovery stages of cyanosis.[3] Improvements in the procedure for the determination of methemoglobin, and disclosure of significant differences between the Hb values found by the acid hematin and oxidation procedures, when applied to exposure cases, have provided the means for detecting the approach of cyanosis conditions before methemoglobinemia develops.[4] These improved procedures applied routinely to operators and mechanics employed in unit operations involved in the manufacture of nitrobenzene and aniline derivatives not only disclosed acute exposure conditions which required correction, but also chronic subcyanosis absorption. Within four years, the general Hb levels were depressed below acceptable limits. Both the increased incidence and severity of cyanosis, and the origin of the Hb decline appeared to coincide with the start of chloroaniline production and increased usage of para-nitroaniline (Figures 1 and 3).

Criteria

A blood specimen was considered to be abnormal if:

1. Methemoglobin (MHb) exceeded 10%.
2. The differences between the acid hematin (AHb) and oxidized hemoglobin (HbM) values for hemoglobin (Hb) were classified as "hemoglobin complexes" (HbC) which were considered abnormal above 10%.
3. The hemoglobin value by either method dropped below 13.0 grams Hb per 100 ml blood—caution limit.[4]

Two consecutive Hb results which repeated weekly fell below 12.0 grams required removal of the patient from further exposure until the average pre-exposure level was regained. During the period of this study, no significant alterations were made in the AHb procedure for the determination of Hb.[5] Trend lines were established by the method of least squares.

When the average Hb level for a work crew ranged between 14.0 to 15.0 grams Hb per 100 ml blood (14.5 ± 0.5 grams/100 ml) control over chronic exposure to chemicals which reduce the Hb level in the blood stream was considered satisfactory ("Satisfactory Hb Level"—Figures 1 to 5).

The number of cyanosis cases incurred on an

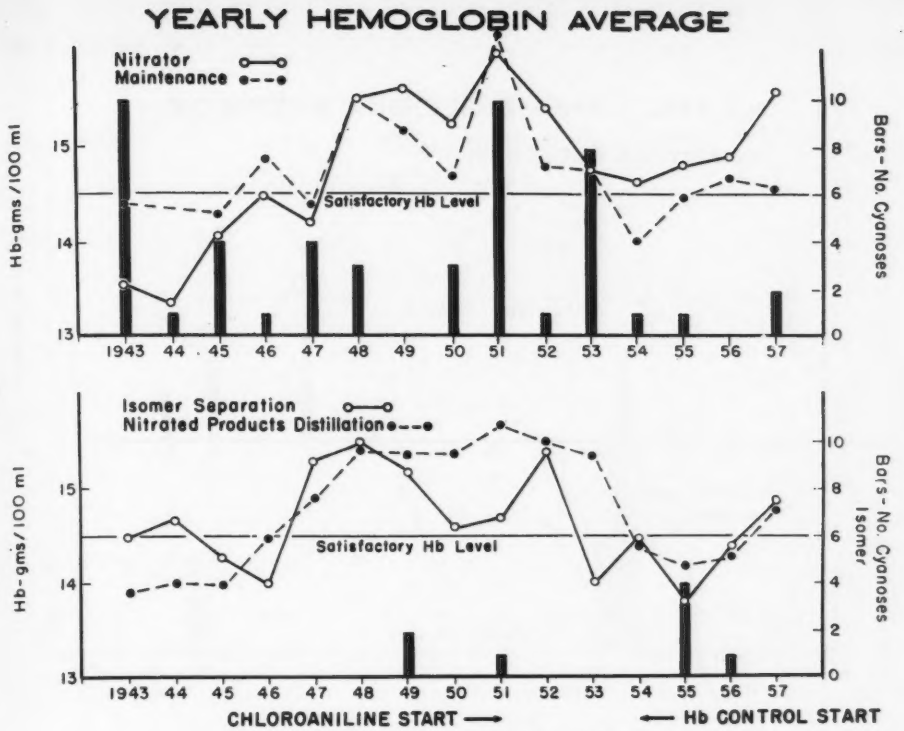

FIGURE 1. (Top.) FIGURE 2. (Bottom.)

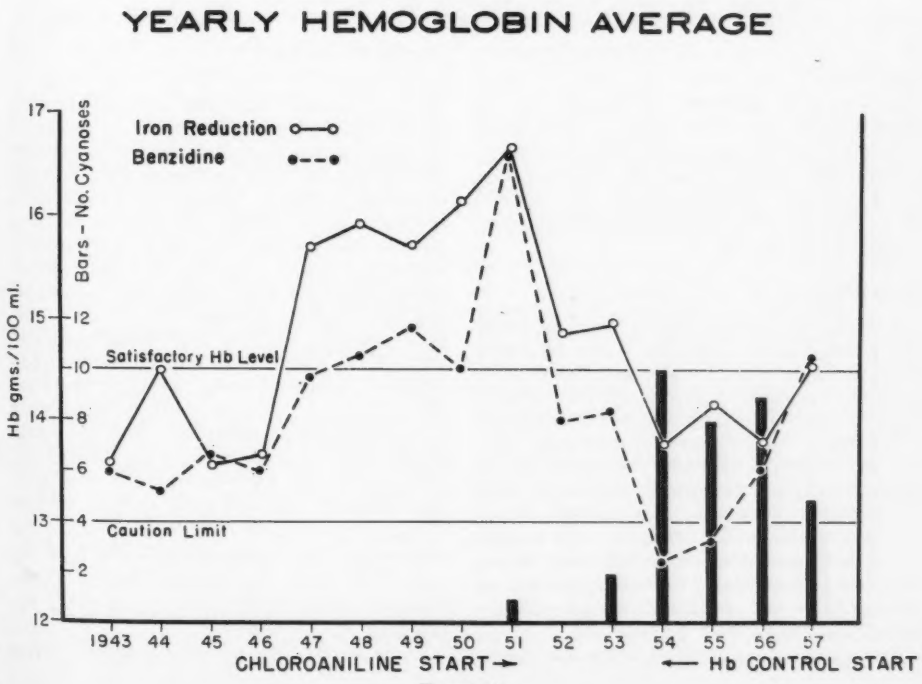

FIGURE 3.

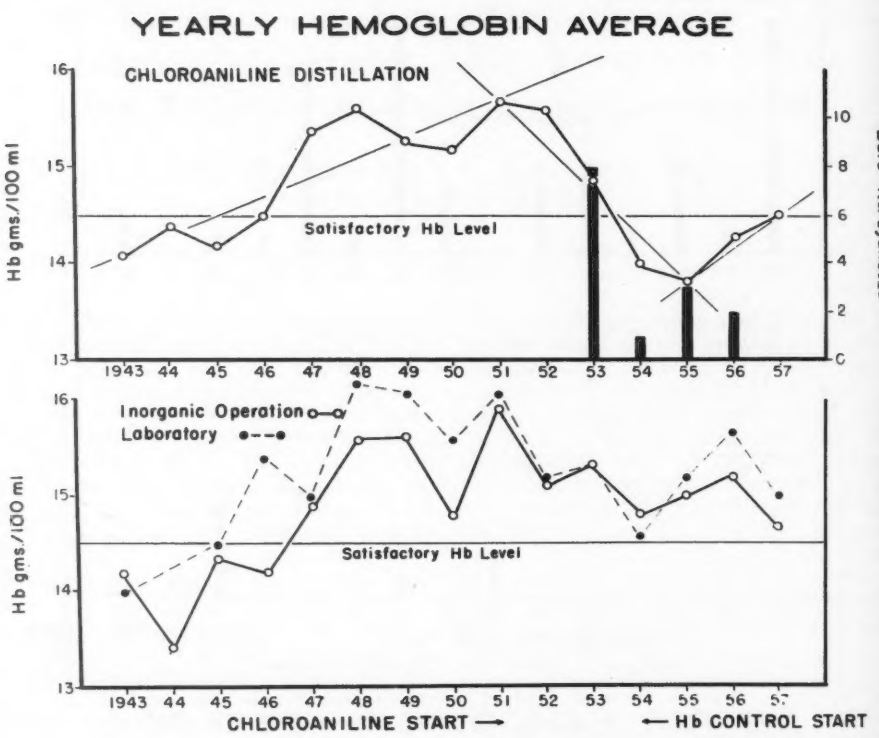

FIGURE 4. (Top.) FIGURE 5. (Bottom.)

annual basis is indicated by vertical bars in Figures 1 to 4, and 7. The incidence of abnormal hemoglobin conditions as defined by criteria 1, 2, and 3 above, in blood specimens collected from any given crew was expressed as "% Abnormal Blood Specimens". Examples are presented in Figures 6 to 8, and 10.

Acute Phase

Although cyanosis has been a major industrial health problem on Chambers Works for many years, no fatalities attributable to this cause have occurred. Following an all-time high of reported cases in 1940–1941, a steady downward trend ended with a sharp upward break in both numbers and severity in 1951 with the start of chloroaniline production (Figures 1, 3, and 4). With recognition of the potency of this aniline derivative, new to the production areas, came realization that control measures satisfactory for the toluidines, phenetidines, alpha-naphthylamine, nitrotoluidines and anisidines were not effective enough for chloroaniline manufacture.

An incident which occurred in the iron reduction unit clearly illustrates this new problem (Figure 6). A graph of the Hb history of a maintenance crew working on a chloroaniline stripper during May and June of 1956 gave the first hint of trouble on May 23–24 when 100% of the blood specimens were abnormal. On May 28, two mild cases of cyanosis developed. On May 31, production was shifted to ortho-toluidine. Immediately the percentage of blood abnormals dropped below 15%. Since no precautions were taken to reduce exposure severity, this "break" indicated that ortho-toluidine is an aniline derivative possessing a relatively weak cyanosis potential. When chloroaniline production was started again June 12, blood abnormals rose to 60%. During the following day, a mild case of cyanosis developed, then on June 14, three severe cases of cyanosis were incurred. In each case, at least 24-hour warning was available from the high percentage of abnormal blood specimens collected from this crew. This experience furnished the basis for an exposure control system based upon a 30% upper limit for abnormals.

Study of the Hb analyses compiled during

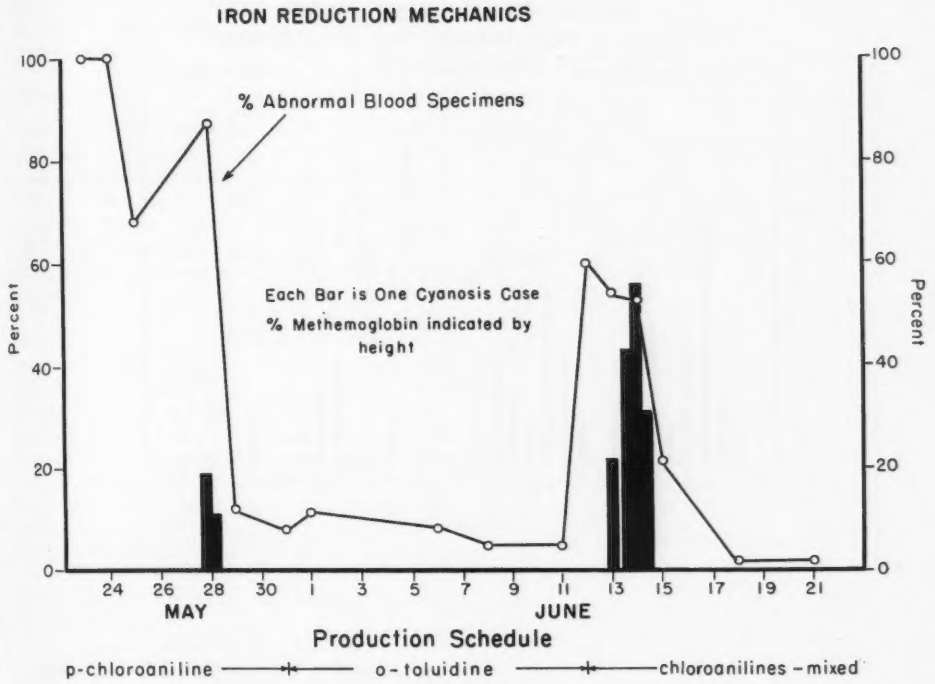

FIGURE 6.

1955–1957 disclosed an approximate relationship between the percentage of abnormal specimens and the number of cyanosis cases for the entire production line on a monthly basis (Figure 7). This downward slope nearly parallels the decreasing cyanosis trend from the initiation of exposure control in mid 1955 through 1957.

A more definite correlation was derived by relating the cyanosis frequency (expressed as percentage of cyanosis cases detected) to the percentage of abnormal specimens above which these cases occurred (Figure 8). This relationship showed promise as a means for estimating the probability of cyanosis-free periods for any given control limit. The chart indicates 20% would be a more realistic limit than the original 30% estimate. At the 20% level, 70% of the cyanosis producing conditions would be detected, and the "All Clear" would fall within a reasonable range; i.e., only three in ten chances that an undetected cyanosis case would develop. If less than 12% of the specimens are abnormal, cyanosis would not be expected to develop in the group sampled.

Since heat has been recognized for some time as a major factor in the development of methemoglobinemia, the cyclic nature of the monthly cyanosis incidents within annual groups was examined for ambient temperature effects. A linear relationship, within surprisingly close tolerances, between cyanosis frequency and ambient temperature was derived from the data in Figure 7 (Figure 9). At 30°–35°F an apparent anomaly was found. However, consideration of the probable circumstances led to the conclusion that under these conditions, work would be carried out in heated buildings where there would be little thermal relationship to outside ambient temperature. Following a vertical from the anomalous point to the curve, an intersection in the 65°–70°F interval, the expected normal winter indoor temperature, was obtained.

Temperature is undoubtedly one of the major influences responsible for the failure of severe exposures to aromatic nitrocompounds, detected by urine analysis,[3] to produce HbC and MHb during winter months. Cyanosis from lesser exposures often develops rapidly under conditions of elevated ambient temperature in drier rooms, near steam stills, after hot showers at shift end, etc.[4] This temperature effect may be responsible for the "false positives" encountered in applying

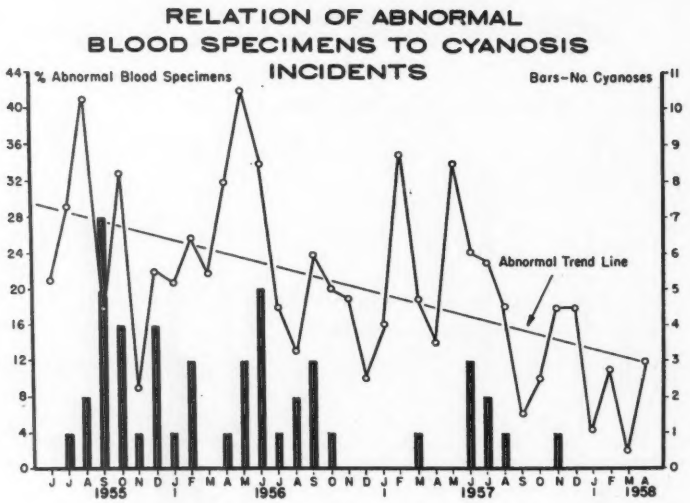

FIGURE 7.

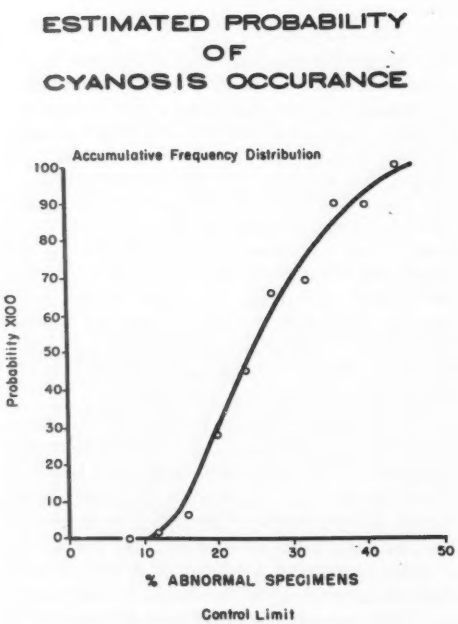

FIGURE 8.

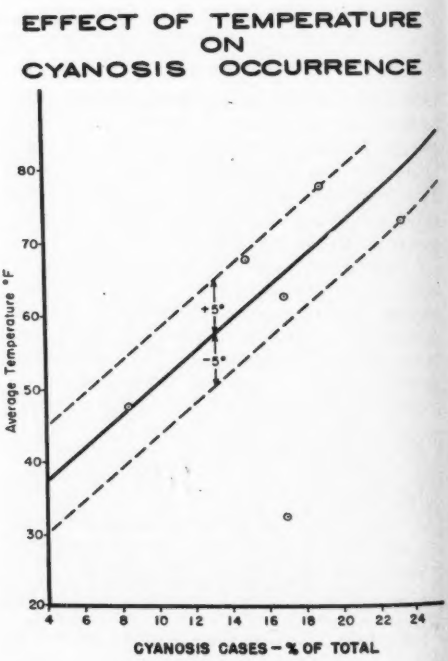

FIGURE 9.

the control limits indicated by the probability curve (Figure 8).

Chronic Phase

Plots of the Hb values, averaged on an annual basis for each of the unit operations and the maintenance crew, disclosed a steady rise from a low during the war years (1943–1946) to a peak level in 1951 (Figures 1, 2, 3, 4, and 5). This rise was due in part to reduced tension, improved living habits, improved equipment maintenance, better process control and the addition of new employees—literally introduction of fresh blood. In 1951, the production of chloroanilines on a large scale was started in the Iron Reduction unit. The depressing effect on Hb levels was apparent within two years, not only in the reduction operations, but also in all of the supporting units engaged in the manufacture and purification of nitrochlorobenzenes required for reduction. However, in every case, the average Hb levels had returned to the satisfactory median, 14.5 grams/100 ml, by 1957 largely as a result of the rigorous control measures developed and applied by the operating, engineering and medical supervision.

The change in slope of the trend lines derived from the plotted data by the method of least squares was definitely significant for the nitrator, reducer and distillation units (Table I). Extrapolation of the downward sloping trend lines indicated that unless corrective action was taken, the lower Hb control limit, 13.0 grams/100 ml blood, would be reached before 1958. In this region, removal of some individuals would be necessary as the more susceptible would suffer Hb losses below the 12.0 grams lower acceptable limit. Corrective action initiated in late 1953 showed a definite reversal of both average Hb trends and incidence of cyanosis by 1957. However, the control groups continued their downward Hb trends through 1957 (Fig. 5, Table II).

The reaction of the chloroaniline distillation group which had no direct contact with aromatic nitrogen compounds prior to 1951 is especially noteworthy (Figure 4). The superposed trend lines not only illustrate the post 1951 Hb decline, but also show a definite recovery trend after 1955 when exposure control measures became effective. The characteristic delay in Hb recovery after bringing cyanosis under control also is illustrated by the parallelism between the 1951–1955 declines for both cyanosis incidence and Hb concentration.

No significant general trend could be determined by least squares analysis of the isomer separation Hb history (Figure 2). Rather frequent transfers, and fluctuations in production schedules undoubtedly are responsible for amplification of the deviations in this small crew. However, at least one excessive exposure incident (1955) was associated with the installation of a new piece of equipment which in its original design did not incorporate sufficient exposure control features. This also affected unfavorably the nearby distillation unit.

Differences in magnitude which clearly designated the areas of severest exposure were obtained from the yearly average Hb data (Table II). The minimum Hb levels, % Hb loss, rate of Hb loss, and cyanosis incidence from Table II arranged in columns of increasing severity ("Rank"), and addition of the four numbers cor-

TABLE I

Statistical Development of Trend Lines
By Least Squares Method

Figure	Number trend lines	Degrees of freedom	Range in years	Variance S^2	F	Critical F level 5%	No. trend lines confirmed
1	1	13	1943–1957	0.408	—	—	
	3	9	'43–'51–'54–'57	0.123	3.30	3.06	3
	Cubic	11	1943–1957	0.242	1.69	2.76	
2	1	13	1943–1957	0.337	—	—	
	2	11	'43–'51–'57	0.185	1.83	2.76	1 or 2
3	1	13	1943–1957	0.294	—	—	
	3	9	'43–'48–'55–'57	0.231	1.27	3.06	1
4	1	13	1943–1957	0.420	—	—	
	2	11	'43–'51–'57	0.120	3.49	2.76	2
5	1	13	1943–1957	1.156	—	—	
	2	11	'43–'51–'57	0.443	2.61	2.76	1 or 2
6	1	13	1943–1957	1.038	—	—	
	3	9	'43–'51–'54–'57	0.316	3.29	3.06	3
7	1	13	1943–1957	0.454	—	—	
	3	9	'43–'51–'55–'57	0.099	4.58	3.06	3
8	1	13	1943–1957	0.447	—	—	
	2	11	'43–'51–'57	0.197	2.28	2.76	1 or 2
9	1	12	1943–1957	0.331	—	—	
	3	8	'43–'51–'54–'57	0.201	1.65	3.28	1 or 3
10	1	12	1943–1957	0.421	—	—	
	2	10	'43–'51–'57	0.213	1.98	2.91	1
	2	10	'43–'48–'57	0.175	2.41	2.91	1 or 2

X = Year

Y = Hb

$\bar{X}$ = Yearly average

$\bar{Y}$ = Hb average

$\hat{Y}$ = Calculated

$$Y = b^0 + b_1 X$$

$$b_1 = \frac{n\Sigma XY - \Sigma X \Sigma Y}{n\Sigma(X^2) - (\Sigma X)^2} = \text{Slope}$$

$$b^0 = \bar{Y} - b_1 \bar{X}$$

$$\text{Variance} = \frac{\Sigma(Y - \hat{Y})^2}{n - 2}$$

TABLE II

Operation	No. men in crew		1943	Peak Hb Level		Low Hb Level		% Hb Loss	Rate gms/ Year	1957 Hb regain		No. cyanosis after 1950
	Actual	Sampled	Hb Level	Year	gms/100 ml	Year	gms/100 ml			gms	%	
Nitration	29	15	13.5	1951	16.0	1954	14.6	8.8	0.48	15.6	6.9	23
Nitrated Prod. Dist.	5	6	13.9	1951	15.7	1955	14.3	8.9	0.35	14.8	3.5	0
Isomer separation	7	6	14.5	1952	15.4	1955	13.8	10.4	0.53	14.9	8.0	6
Iron Reduction	9	9	13.6	1951	16.6	1954–56	13.7	17.5	0.97	14.5	5.8	35
Benzidine	4	4	13.5	1951	16.6	1954	12.6	24.0	1.33	14.6	15.9	(1)
Chloraniline Dist.	13	11	14.1	1951	15.7	1955	13.8	12.1	0.48	14.5	5.1	14
Hydrogen reduction	28	30	14.3	1951	16.1	1956	14.1	12.4	0.40	14.8	5.0	10
Maintenance	29	(27)	14.4	1951	16.2	1954	14.0	13.6	0.73	14.6	4.3	(26) (2)
Total	—	125	—		—		—	—	—	—	—	88
Averages		—	14.0	1951	16.0	1954–56 Control	14.0	12.5	0.56	14.8	5.7	—
Inorganic Chem.		26	14.2	1951	15.9	1957	14.7	7.5	0.20	14.7	0.0	0
Laboratory		18	14.0	1948	16.2	1954	14.6	9.9	0.27	15.0	2.7	0
Total		44	—		—		—	—	—	—	—	
Averages		—	14.1		16.0		14.7	8.1	0.23	15.1	2.0	

Notes

(1) Included in Iron Reduction

(2) Included in Production units—calculated from percentage, 29, of total cyanosis cases charged to Maintenance Post 1950

TABLE III

Summation of Rankings from Table I in Order of Increasing Severity (1-Least, 10-Most)

Rank No.	Minimum hemoglobin level	Percentage hemoglobin loss	Rate hemoglobin loss	Number cyanosis cases	Summation	
					Rank sum	Location
1	Inorganic	Inorganic	Inorganic	Inorganic	4	Inorganic
1	—	—	—	Laboratory	9	Laboratory
1	—	—	—	Nitro Dist.	10	Nitro Dist.
2	Laboratory	Nitro Dist.	Laboratory	—	19	Nitration
3	Nitration	Nitration	Nitro Dist.	—	21	Hydrogen Red.
4	Nitro Dist.	Laboratory	Hydrogen Red.	Isomer Sep.	23	Isomer Sep.
5	Hydrogen Red.	Isomer Sep.	Chloroaniline Dist.	Hydrogen Red.	25	Chloroaniline Dist.
6	Maintenance	Chloroaniline Dist.	Nitration	Chloroaniline Dist.	30	Maintenance
7	Isomer Sep.	Hydrogen Red.	Isomer Sep.	Nitration	36	Iron Red.
8	Chloroaniline Dist.	Maintenance	Maintenance	Maintenance	39	Benzidine
9	Iron Red.	Iron Red.	Iron Red.	Iron Red.		
9	—	—	—	Benzidine		
10	Benzidine	Benzidine	Benzidine	—		

responding to the position of each production unit within each column ("Rank Total") yielded a chronic exposure severity series ("Location"—Table III) when arranged in order of increasing magnitude.[6]

Exposure Control

A statistically significant number (preferably not less than four) from each crew working in areas of potentially severe exposure hazard were examined routinely each day for Hb analysis. At the end of the day, the percentage abnormals were calculated, and if the 30% control limit was exceeded, supervision of the crew was notified, and appropriate action suggested. Two examples of the effectiveness of this type of control are given in Table IV for an area where severe cyanosis episodes had occurred in the absence of such control measures (Figure 4).

The Hb analyses needed for chronic exposure control were collected from operators and mechanics:

1. Routinely on a quarterly basis,
2. Whenever these employees report to the Medical Building for observation of traumatic injury,
3. Personal illness.

Any patient who exhibited a MHb level above 10% received close medical supervision, and was not returned to his assigned job until the attending physician was satisfied recovery from the episode was complete. When the HbC value exceeded 15%, the Hb control analysis was repeated, preferrably within two hours but no later than 24 hours, to determine whether the aromatic nitrogen metabolism cycle was progressing toward methemoglobinemia, or the natural defensive processes were restoring the blood to normal conditions. If both Hb procedures indicated a fall in the 12.0–13.0 grams range, repeat analyses were carried out weekly to detect downward trends which required medical attention.

Since routine tests from any given unit operation did not furnish, on a daily basis, sufficient data for an evaluation of cyanosis exposure control, Hb results were examined on a weekly and monthly basis. The building supervision was advised when the abnormal trend reached 30%.

The application of blood analysis to the solution of an exposure problem by evaluation of severity at sub-cyanosis levels is illustrated in Figure 10.

A plot of the MHb, HbC, and % abnormals at frequent intervals for each operator on day shift furnished the following information:

1. Those pieces of equipment, or routine operations which repeatedly produce excessive exposure. This pinpointing confirmed the major sources of product loss for effective expenditure of maintenance, process revision, and design improvement funds to alleviate the unsatisfactory working environment, and conserve materials.
2. Evaluation of work habits of either individuals or shift crews.
3. Detection of individuals unusually susceptible to hemoglobin damage.
4. Estimation of the relative cyanosis producing potentials of aniline derivatives. Chloroanilines, and 2-chloro-4-aminotoluene were approximately equivalent, whereas 2,5-dichloroaniline appeared to be somewhat less potent.
5. Air analysis (either nitro or amino compound), and blood analysis did not correlate within limits which justify use in exposure evaluation. These fat soluble compounds are absorbed mostly by direct skin contact with contaminated surfaces, and steam borne mists. Again, confirmation of the industrial hygiene principle "Man himself is the best sampler of his environment".

Reduction of exposure below levels which produce physiologically undesirable absorption can be attained by five practical control procedures, arranged in order of increasing effectiveness:

1. Respiratory protection. Canister masks, air supplied masks, and dust respirators alone have a very limited utility since alleviation of skin absorption is the major problem.
2. Rotation of the members of the work crew. This is an example of minimal abnormal hemoglobin control limit which requires numerous daily blood analyses to determine which men are to be removed to areas of less exposure. This procedure could be applied only to the Construction Department where a variety of jobs was available.
3. Limited exposure duration. Limitation of working time in contaminated areas was practical only for maintenance crews, and operators involved in unusual job incidents. The production time lost, numbers of men involved, loss of contaminated clothing, especially gloves and shoes, uncertain magni-

TABLE IV

Blood Analysis for Prevention of Cyanosis
Chloroaniline Still Repairs

Date	Blood Analysis		Status of Exposure Control	Remedy
	No. Spec.	% Abnormal		
2–13–58	4	25	Questionable-Super. notified	"Chem-Proof Air Suit"
2–14–58	5	0	Satisfactory	"Chem-Proof Air Suit"
2–15–58	18	17	Satisfactory	"Chem-Proof Air Suit"
2–16–58	—	—	Day Off	
2–17–58	6	33	Not satisfactory-Super. notified	Rotated crew—"CPA Suit" use re-instated
2–18–58	4	0	Satisfactory	Different craft involved
MCA Still Column Repairs				
5–14–58	4	25	Questionable	Man KOA'd—super. notified
5–15–58	6	16	Within limits	Man KOA'd—"CPA Suit" recom.
5–19–58	12	8	Satisfactory	"CPA Suits" in use
5–20–58	9	22	Questionable	Crew rotation—super. notified
5–21–58	9	11	Within limits	"CPA Suits"—column sandblasted
5–22–58	4	0	Satisfactory	Reduced exposure
5–23–58	10	10	Satisfactory	Reduced exposure
Operators				
5–20–58	3	33	Unsatisfactory	Super. notified
5–21–58	2	0	Satisfactory	Reduced exposure

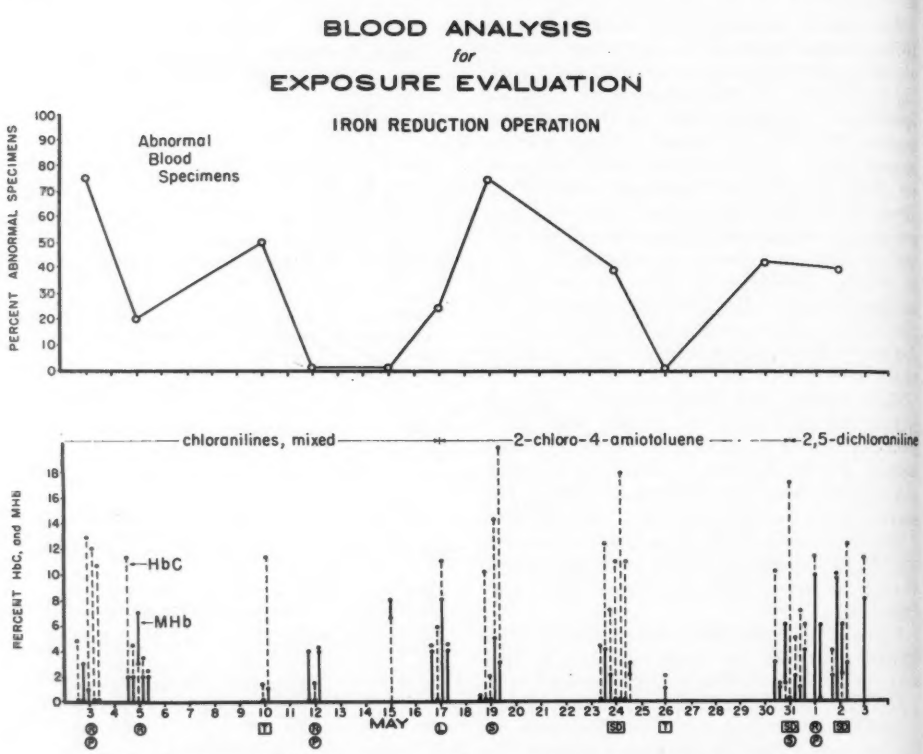

FIGURE 10. Circles indicate known leaks. Squares indicate clean-out jobs. R-Reducer kettle. S-Steam still. L-Reducer feed line. P-Pump. T-Storage tank. D-Clarification filter.

tude of exposure hazard, and poor labor efficiency render this alternative unattractive even for special jobs. The questionable effectiveness of job limitation in selecting bricklayers and lead burners for overtime in an emergency tank repair job is illustrated in Table V.

4. Use of butyl rubber protective equipment, such as gloves, overshoes, sleeves and aprons consistently on a routine basis, can reduce exposure within acceptable limits for all but the unusual incidents. No other commercially available elastomer approaches butyl rubber in resistance to penetration by aromatic nitro and amino compounds.[7]
5. Complete body protection for severe exposure conditions. Application of the "Chem-Proof Air Suit,"[7] an air-conditioned garment impervious to the neck line, and provided with air supplied helmet and cape which integrates head and body coverage as a single unit, has eliminated cyanosis at locations such as the chloroaniline distillation unit (Table IV).

In addition, a continuing intensive educational program has been estabished to create respect for the hazard, an understanding of the cause and effects of cyanosis and acceptance of the necessary precautions as a way of industrial life. Lectures, supplemented with visual aids and actual demonstrations of protective clothing have been found essential to the success of this control program.

Summary

ACUTE EXPOSURE

A plot of blood analysis results from a maintenance crew working in the iron reduction area revealed a significant relationship between hemoglobin abnormalities and the occurrence of cyanosis. Precursors could be detected sufficiently

TABLE V

Limitation of Mononitrochlorobenzene Exposure For Overtime Tank Repair—Nitration Operation

(KOA—Keep out of area)

Date	First shift % MHb		Disposal	Second shift % MHb		Man	Remarks
	Before	After		Before	After		
Bricklayers							
10-7-53	4	3	—	—	—	S	
10-8-53	4	10	KOA	—	—	S	
10-7-53	7	7	—	—	—	B	
10-8-53	6	6	KOA	—	—	B	
Lead Burners							
10-8-53	—	12	KOA	—	—	Q	Worked double in the shop
10-9-53	3	—	—	—	—	Q	
10-8-53	—	9	KOA	—	—	V	
10-9-53	—	—	No Spec.	—	4	A	
10-8-53	—	3	OK'd	3	13	C	Excessive exposure
10-8-53	—	3	OK'd	3	12	F	Excessive exposure
10-9-53	—	7	KOA	—	—	J	
10-8-53	—	—	No Spec.	—	12		Excessive exposure, no control specimen

in advance to serve as a warning to reduce exposure severity before methemoglobinemia developed. Experience accumulated during the following eighteen months has confirmed the appearance of more than 30% hemoglobin abnormalities at least 24 hours preceding cyanosis episodes in those groups from which a statistically valid number of specimens were received.

Over-all laboratory data plotted on a monthly basis revealed locations which needed corrective measures to reduce absorption, detected seasonal ambient temperature effects, and provided long term hemoglobin concentration trends. The steadily declining trend for both cyanosis occurrences and abnormal hemoglobin from 1955 through 1957 indicated that exposure control measures adopted were effective, and suggested a reduction in permissible abnormal specimen limit to 20% for maximum performance. The study also demonstrated differences in cyanosis producing potentials between chloroanilines and toluidines.

CHRONIC EXPOSURE

Charts of the yearly averages of all blood analyses carried out for the operating crews engaged in the manufacture of aromatic amines, and aromatic nitrocompounds required for its production by iron reduction disclosed a rising trend in hemoglobin concentration from 1943 to a peak in 1951. A break to a distinct downward trend coincided with start of chloroaniline production in 1951. The rate of decline was approximately proportional to the increase in rate of manufacture to 1956 when production fell off. The effects of process and equipment improvements, and exposure control measures introduced in late 1953 to alleviate cyanosis initiated a recovery trend.

Acknowledgment

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Review of Cascade Impactors for Particle Size Analysis and a New Calibration for the Casella Cascade Impactor*

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Introduction

A CASCADE impactor is an air sampling device consisting of high velocity jets in cascade or series, with each jet directing the air against a collecting plate at a progressively higher velocity. As a result, each stage is capable of collecting smaller particulates than the preceding stage. The first published description of such a device was by May[1] in 1945. It was a four-stage collector designed to take samples of droplet aerosols in natural winds, and was effective for collecting particles of unit density in the size range 50μ to 1.5μ. Liquid droplets were collected effectively on plain glass slides, but solid particles required an adhesive layer on the slide to prevent re-entrainment. The samples could be analyzed by microscopic counting and sizing, or by using a characteristic size for each stage as determined by calibration, the approximate size-mass distribution of the aerosol could be obtained from the percentage of the total mass collected on each stage. This latter method intrigued people interested in the size distribution of air-borne particulates. Here was a method of particle sizing with many advantages over existing methods, including:

1. Particle size analyses could be performed with a series of mass determinations, rather than with the time-tested but tedious standard method of individually sizing several hundred dust particles on a microscope slide. The mass analysis could be a colorimetric or other chemical determination, a radiometric count, or any other procedure suitable to the material being studied.
2. The size distribution of one component of an aerosol could be determined in situations where the presence of background particulates would prevent accurate sizing by optical or sedimentation methods.
3. The size distribution of dusts which are altered by the process of collection, or which decompose or decay following collection, could be determined. A cascade impactor grades an aerosol on the basis of its air-borne particle size, and as long as some fraction or derivative of the original material remained on the slides, the size analysis would be the same as if the material were unchanged from its air-borne state. Thus, particles which swell or shrivel; or droplets which spread, or coalesce, or partially evaporate; could be analyzed.
4. The particles are graded by their effective aerodynamic diameter in both the cascade impactor and the respiratory system, since similar processes of inertial impaction take place in both cases. For nonhygroscopic aerosols, the particles collected on stages 1 and 2 are those which would be removed in the upper part of the respiratory system, regardless of the particle density or shape, while the particles on the remaining stages are those which penetrate to the alveolar spaces.

As a dust sampling system, a cascade impactor is far superior to a single-stage impactor. In order for a single-stage impactor to collect the smallest particles collected by a cascade impactor, the jet velocity would be high enough to shatter many of the larger particles. In addition, there is a tendency for the larger particles to be blown off a high velocity jet impactor stage after they have been collected. In a cascade impactor these larger particles would have been removed by the low velocity stages, where they would be less subject to re-entrainment. Davies, Aylwood, and Leacey[2] have presented an excellent discussion of these phenomena.

Because of the advantages cited, many industrial hygienists adopted the cascade impactor as a particle sizing device. Since the May impactor was not designed for sampling aerosols with the particle size range and concentration of industrial aerosols, it had several short-comings and limitations when used for such pur-

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poses. These included poor collection efficiency for submicron particles and limited collection capacity. Many modifications of the May impactor have appeared since 1945. In these, attempts were made to design an instrument more suitable for sampling industrial aerosols.

Review of Cascade Impactors and Their Calibration for Particle Size Analysis

A modified version of the May impactor has been manufactured by Casella[3] since about 1948. The only changes from the original were a reduction in the slit widths of the third and fourth jets, and provision for separating the stages for cleaning and repair. In 1959, Casella put a revised version on the market. To the author's knowledge, the Casella impactors are the only commercially available instruments.

May calibrated his original impactor and its first Casella modification by optically sizing droplets of unit density collected on the four stages. He measured the diameters of the lenses formed when the spherical droplets struck the collecting slide, and then applied a correction factor to translate the lens diameter to the original droplet diameter. The results were expressed as curves of percentage of drops penetrating versus droplet diameter. In addition, May tentatively suggested the use of a characteristic size for each of stages 2, 3, and 4, which he called effective drop size (EDS), and defined as being the diameters of drops (or solid particles if nearly spherical and of unit density) which, when plotted against the percentage of the total mass collected up to and including the corresponding slide, give an approximation to the cumulative mass distribution curve. The values were calculated by an empirical process. The figures were the average ones by which the optically-counted mass distribution curves were best fitted by the relative masses on the stages, from a considerable number of spray samples. For the original May impactor, the EDS values for unit density particles were given as 14.5, 4.0, and 2.5μ for stages 2, 3, and 4, and for the Casella version were 13, 4.0, and 1.7μ. No figures were given for stage 1, since it would be dependant on the maximum size present in the aerosol.

By means of dimensional analysis, May developed a generalized impaction parameter I, defined as:

$$I = \frac{\rho V D^2}{\eta l}$$

where: ρ = particle density—gm/cc

V = velocity of jet—cm/sec

D = diameter of particle—cm

η = viscosity of air—poise

l = width of jet—cm

Applying his experimental data to this equation, May found that the values of I for a given impaction efficiency were approximately constant, with an average deviation from the mean of about 15% over a twelvefold range of D. Although May did not specifically suggest that EDS could replace D in this relation, many investigators have made the substitution in order to apply the EDS concept to particulates with other than unit density. The accuracy that could be obtained when using such calculated stage calibration values for the size estimation of industrial aerosols is questionable. It is dependent upon the extrapolation, by means of an inexact theoretical relation, from a method described by May as a "rough and ready estimation." It involves the translation of data obtained with spherical liquid droplets of unit density to irregular solid particles with densities several or many times greater. When applied to industrial dusts, the results obtained with this procedure would be very rough and ready estimates indeed.

In 1946, Sonkin[4] described a four-stage handmade glass impactor with considerably higher jet velocities than the May impactor. The purpose of the higher velocities was to impact smaller particles. The procedure used for calibrating this instrument was not described in detail.

In 1949, Laskin[5, 6] of the University of Rochester's Atomic Energy Project described a five-stage cascade impactor machined out of brass. It consisted of four slit impaction stages, with jet dimensions patterned after the original May impactor, and a filter paper as the fifth collection stage. With the filter paper following the impaction stages, all of the dust in the sample could be collected and the fraction of the dust on each stage could be determined accurately. Detailed drawings were made available and many investigators constructed impactors to the University of Rochester design. Many others[7, 8] added filter paper stages to Casella impactors.

Laskin had attempted to calibrate the May impactor for UO_2 dust by optically sizing samples collected on stages 2, 3, and 4 with slides coated with a non-drying alkyd resin adhesive layer. From this work, he concluded that direct

optical sizing of samples collected on coated slides was unsatisfactory because the resolution of submicron particles was not possible either with an oil immersion objective and a resin mount, or a hi-dry objective with a dry air mount. In the former case, the difference in refractive index between the mounting medium and collected dust was too small for the submicron particles to be seen. For an air mount, the difference in refractive index between the air and the dust was high enough, but the theoretical limit of resolution for a hi-dry objective is only about 0.7μ. Based on these conclusions, he developed and used an indirect opticle sizing method in calibrating his machined brass impactor.

To improve resolution, he increased the refractive index difference by vacuum-evaporating coatings of selenium (refractive index = 2.8) over dust deposited on a glass slide. This made all particles down to about 0.2μ readily visible under an oil immersion objective. However, the selenium coating could not be applied to samples collected on adhesive covered slides. In order to obtain an calibration equivalent to that for resin coated collecting slides measured with selenium coating, three different calibrations were made and graphically combined. In Method 1 samples were collected on resin coated slides and measured as resin mounts; in Method 2 samples were collected on uncoated slides and measured as resin mounts; and in Method 3 samples were collected on uncoated slides and measured as selenium mounts. Method 2 was corrected by the results of Method 3 to take advantage of the more accurate measurement technique afforded by selenium coating, and was corrected by the results of Method 1 to take advantage of the higher collection efficiency obtained by use of resin coated collecting slides. The three methods were assumed equivalent in other respects, and the effects, if any, of particles fracturing on, or being re-entrained from, the uncoated slides were assumed to be negligible. Using this procedure, Laskin sized samples of UO_2 dust and determined characteristic diameters for each stage, defined as the mass median diameter (MMD) of the dust collected on that stage. Based on the theory that the product of particle density and the square of particle diameter is a constant, he presented a series of curves of MMD versus particle density to permit the UO_2 calibration to be extended to other dusts.

The applicability of this calibration of the Laskin impactor to the Casella impactor is restricted by the following considerations:

1. The jet dimensions of the two instruments are different, and do not vary from stage to stage in the same manner.

2. The recommended flow rates are different. The Laskin instrument is used at 14.0 lpm and the Casella at 17.5 lpm.

3. They have slightly different jet-to-slide clearances, geometrical proportions, etc. Very likely, there are differences in wall losses and air leakage locations, etc.

These limitations can be largely overcome by a comparison calibration with Laskin and Casella impactors. If both are run simultaneously in the same atmosphere, the Casella stage constants can be defined from the orignal Laskin calibration data. Los Alamos[8] and other laboratories have calibrated Casella impactors by this procedure.

Hyatt, Moss and Shulte[9] of the Los Alamos Scientific Laboratory described the use of Laskin-type impactors and Casella impactors in particle size studies of uranium machining and metallurgy operations. Both types were calibrated against a standard Laskin impactor at the University of Rochester, and the Laskin method was used in treating the data obtained. The authors also reported the experimental results of an alpha track counting procedure used to estimate the size distribution of enriched U_3O_8 aerosols. The samples were collected with a cascade impactor and the size distributions were calculated from the track counts and also measured optically. Results were reported on two stage 1 and two stage 2 slides. The experimental MMD's on stage 2 were 5.7 and 4.1μ by track count, and 8.6 and 6.5μ by optical sizing. These values are quite different from the mass median diameter of 2.08μ derived from the Laskin calibration as a constant for stage 2. They are, however, in fair agreement with the stage 2 mass median of 6.6μ established by the experimental work to be described in this paper.

In 1951, Ranz and Wong[10, 11] of the University of Illinois, discussed the behavior of aerosols passing through jet impactors. They attempted, through theoretical considerations, to define the impaction process with an inertial parameter ψ (essentially similar to May's I factor), which represented the ratio of stopping distance to aerosol jet diameter. When $\psi = 1$ all particles should be impacted. ψ was defined as:

$$\psi = \frac{C\rho_p V_0 D_p^2}{18\mu D_c}$$

where: $C = 1.00 + \frac{0.16 \times 10^{-4}}{D_p}$

ρ_p = particle density—gm/cc

V_0 = jet velocity—cm/sec

D_p = particle diameter—cm

μ = viscosity of air—poise

D_c = jet width or diameter—cm

In their experimental work, the authors generated monodisperse glycerol aerosols and sampled them with both round and rectangular impaction jets using various flow rates and particle sizes. They plotted $\psi^{1/2}$ versus collection efficiency, and their experimental data followed sigmoid curves. For rectangular jets the curve gave a $\psi^{1/2}$ value of 0.57 for a collection efficiency of 50%. This value was designated as the characteristic $\psi^{1/2}$ and was used to determine the characteristic particle diameter for any given impactor stage by calculation from the equation. The authors gave two illustrative examples of how this concept would be used in determining particle size with a cascade impactor. They constructed cascade impactors consisting of four impaction stages and a filter. With these, they sampled polydisperse aerosols of NH_4Cl fume and H_2SO_4 droplets. The characteristic diameter for each stage, defined as the size at which 50% of the particles are collected on the stage, was calculated from the physical parameters of the jet and the flow rate, and plotted on log-probability paper against the per cent mass passing that stage. This plot was called a size-mass distribution curve with the 50% intercept being the mass median size. The characteristic diameter D is unquestionably a characteristic of a given impaction stage, and the curve plotted is a size distribution curve of some sort, but the justification for plotting D against per cent escaping impaction and calling the curve obtained a size-mass distribution curve, is not clear.

In 1953, Wilcox[12] of the Army Chemical Center constructed a five-jet cascade impactor patterned after Laskin's.[5, 6] His stages 1, 2, and 3, were identical to stages 1, 2, and 4, of Laskin's, and he constructed fourth and fifth jets of smaller sizes. Apparently this instrument was intended to serve primarily as a particle grading device. No method was given for evaluating over-all particle size distribution.

In 1957, Mitchell and Pilcher[13] of Battelle Memorial Institute, described a cascade impactor consisting of a series of six round jets in a vertical stack, followed by a filter. The design was based largely on the work of Ranz and Wong,[10, 11] and was calibrated with monodisperse aerosols by the same procedure. They obtained a steeper sigmoid curve of $\psi^{1/2}$ versus efficiency, and attributed the difference to the use of a smaller jet-to-slide clearance. As a calibration check, they generated polydisperse aerosols and optically sized the slides from the first three stages. They found that the median particle size on these stages was similar to the size at which 50% of the particles of a monodisperse aerosol would be collected. This was accepted as a verification of the calibration.

In 1958, Brink[14] of the Monsanto Chemical Company described a five-jet in-line impactor similar to the Battelle instrument. The calibration was derived by calculation from the equation and parameters of Ranz and Wong.[10, 11]

Comparison of Size Analyses Obtained from a Casella Impactor Run, Using Applicable Published Calibrations

The calibrations of May,[1, 3] Laskin, [5, 6] and Ranz and Wong[10, 11] can all be applied to the Casella cascade impactor for purposes of comparison. All three sources require different methods of data treatment. May plotted his EDS values for each stage against the sum of the mass per cent on the given stage plus the mass per cent passing that stage. Laskin plotted his MMD (mass median diameter) values for each stage against the sum of half the mass per cent on the given stage plus the mass per cent passing that stage. Ranz and Wong plotted their characteristic diameters for each stage against the mass per cent passing that stage. Thus the stage calibration values obtained from each source represent different parameters and cannot be directly compared. However, if the mass distribution data from a given cascade impactor run is treated independently by each method, the size-mass distribution curves obtained can be compared. The second column in Table I shows the cascade impactor mass distribution obtained from a Casella instrument run simultaneously with a membrane filter in a U_3O_8 aerosol. It also lists the mass per cent values required by each method for plotting an over-all distribution curve, and the calculated stage calibration constants, for each method, for U_3O_8. For the May calibration, the EDS numbers at unit density for the Casella version[3] were corrected to density 8.3. The Laskin calibration MMD's were taken from the generalized curves of MMD versus density for Casella impactors developed by Los Alamos workers[8] from a comparison calibration of Laskin and Casella im-

TABLE I

Stage Calibration Values and Casella Cascade Impactor Mass Analysis for a U_3O_8 Aerosol

Stage	Mass % on stage	May calibration		Laskin calibration		Ranz and Wong calibration	
		E.D.S.-μ	Mass %[a]	M.M.D.-μ	Mass %[b]	(D)-μ	Mass %[c]
1	42.8	—	—	4.55	78.6	6.05	57.2
2	42.8	4.50	57.2	1.90	35.8	1.48	14.4
3	12.2	1.39	14.4	0.81	8.3	0.52	2.18
4	2.07	0.59	2.18	0.41	1.15	0.15	0.11
5	0.11	—	—	0.28	0.06	—	—

[a] Mass % on the stage plus the mass % passing the stage.
[b] Half the mass % on the stage plus the mass % passing the stage.
[c] Mass % passing the stage.

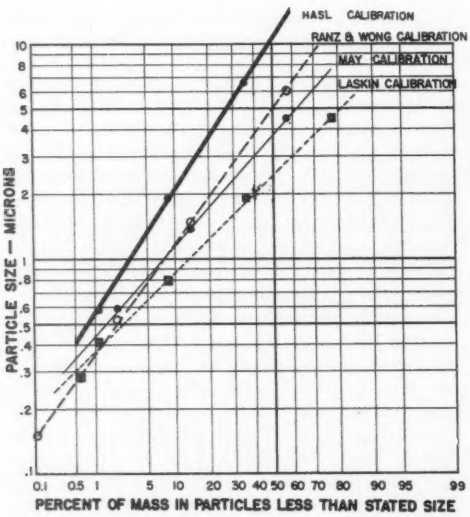

FIGURE 1. Cascade impactor analysis plotted with different stage calibrations.

pactors. The Ranz and Wong characteristic diameters were obtained by calculation from their impaction formula using a $\psi^{1/2}$ of 0.57 and the physical characteristics of the Casella cascade impactor. Figure 1 shows the distribution curves obtained. It can be seen that each curve has a different slope and a different 50% intercept. The simultaneous membrane filter was sized optically and by electron microscope, and the mass median size was calculated from the particle size distribution by the method of Hatch and Choate.[17] The MMD was 11.2 μ by optical microscope sizing and 10.8 μ by electron microscope sizing. From Figure 1 it can be seen that the mass median size was 5.0 μ on the Ranz and Wong curve, 3.8 μ on the May curve, and 2.5 μ on the Laskin curve. Other runs were made but as can be seen from Table II, the agreement between methods was in general no better than in the example cited. This lack of agreement created doubts about the accuracy of all of the previously published calibration data and the applicability of cascade impactors for particle sizing. It appeared that a new calibration study would be needed to determine if the Casella or any other cascade impactor could be used with confidence for particle size determinations.

TABLE II

Comparison of MMD's for Various Aerosols Obtained from Simultaneous Cascade Impactor and Membrane Filter Samples

Test number	MMD's in microns from cascade impactor analyses			MMD's in microns from membrane filter size analyses
	May calibration	Laskin calibration	Ranz and Wong calibration	
A	5.5	3.0	8.2	18.6
B	4.0	2.5	5.2	11.2
C	2.0	1.6	2.4	7.3
D	2.6	1.9	3.2	8.0
E	2.4	1.8	2.8	5.8
F	3.5	2.3	4.5	5.3
G	2.3	1.7	2.7	7.0
H	2.2	1.7	2.7	6.3
I	2.3	1.8	2.8	6.2
J	2.1	1.6	2.5	5.6

Additional Sources of Errors and Limitations of Cascade Impactors

One fundamental limitation of any cascade impactor is that only a limited amount of material can be deposited on any one stage. As a deposit of liquid particulates accumulates, it starts to run off the slide. As a dry deposit accumulates, it becomes more likely that the succeeding particles will strike the particles already deposited, rather than the adhesive coating. Particles striking other particles have a greater tendency to bounce off instead of adhering, and be carried to the next stage, or the walls of the tubes, resulting in an erroneous mass analysis. The fourth stage is usually the first to become overloaded. About 5 μg of sample is the maximum deposit that should be collected on this stage. Thus, the analytical method used must be sufficiently sensitive to detect and measure quantities of one μg or less. The maximum sam-

pling period which may be used before saturation of the adhesive occurs will depend on the concentration and physical characteristics of the dust. Ten-minute samples are generally excessive, even in a relatively clean industrial atmosphere. A visual examination of the impaction slides after a sample has been drawn can give a good indication if the sample was too large. If the deposit on stages 2, 3, and 4, are light single line deposits, the samples are not overloaded. If, however, the line has depth, and certainly if in addition to the major line deposit there is a secondary deposit starting about three slit widths from the major deposit, then an overloaded slide is indicated. Such a sample should be discarded and the impactor should be cleaned before it is used again, since deposition on the walls becomes significant after slide saturation is reached, and subsequent samples could be contaminated by the re-entrainment of this wall deposit. The Harvard Air Cleaning Laboratory[16] found a very large percentage of the dust depositing on the walls of the tubes in their investigation of the Casella impactor, but they were collecting rather heavy deposits on each stage. May[1] reported finding 20% or more of the total sample on the walls of stage 1, but this was due to droplets greater than 50 microns in diameter. He found no deposition on walls of stages 2, 3, and 4.

In an attempt to overcome the short sampling time restriction, May[15] constructed a cascade impactor with moving slides. He placed a rack and pinion carriage under each jet of a Casella impactor permitting the dust deposit to be spread over the length of the slide, rather than limited to the area under the jet. All of the slides were driven simultaneously by a small electric motor connected to the pinion of each stage through sprocket wheels and a common chain. While this modification accomplished its intended purpose, it is unfortunately not commercially available, and would represent a formidable and expensive fabrication problem for most investigators interested in adopting it.

Cascade impactors are inherently incapable of characterizing the size distributions of monodisperse aerosols with accuracy. In an illustrative example, the Harvard group[16] demonstrated that a false distribution curve would be obtained from a cascade impactor analysis of such an aerosol. Approximately the right mass median size was calculated, but the standard deviation was greater than one. The magnitude of this error diminishes as the true standard deviation increases and would be relatively small for most industrial aerosols.

Conclusions from Cascade Impactor Review and Outline of Experimental Investigation

Despite its limitations, cascade impactor size-analysis would be a very useful and convenient method if a reliable calibration was available or could be developed. In order to determine if any of the published calibrations were reliable, and to satisfy other questions raised about the performance and characteristics of cascade impactors, a laboratory investigation was initiated.

The Casella cascade impactor was chosen for this investigation because (a) a number of them were available in the laboratory and (b) the results would find useful application since the Casella instrument is commercially available and widely used. The study's general objectives were: (a) to determine stage calibration constants for various dusts and develop a generalized correlation of size and density, if possible, and (b) to check the results obtained using this calibration against the results obtained using an independent technique. To accomplish these objectives it was decided that the following laboratory analyses would be required:

1. Optical sizing of dust on impaction stages 2, 3, and 4, for dusts of various densities.
2. Determination of the mass quantities collected on all five stages.
3. Optical sizing of membrane filter samples collected simultaneously with the cascade impactor samples.
4. Sizing of electron micrographs prepared from selected membrane filters, as a check on the optical sizing.

From the results of the optical size analyses of the impaction stages, the mass median size for each stage for each dust could be calculated, and the effect of particle density determined. With these stage MMD values and the mass analyses, size-mass curves could be drawn giving the MMD for the over-all aerosol. This could then be compared with MMD for the over-all aerosol determined by calculation from the direct sizing of the simultaneous membrane filter samples.

Apparatus, Procedures, and Treatment of Data

The HASL Modified Casella Cascade Impactor: A modified Casella cascade impactor is shown in Figure 2. The Casella cascade impactors belonging to the Health and Safety Laboratory are not all identical. The tube diameters of several of them (in Casella serial numbers between 526 and 562) are slightly larger than those of others (Casella #994 to 1038). While the stages are interchangeable within each model group, they cannot be interchanged between

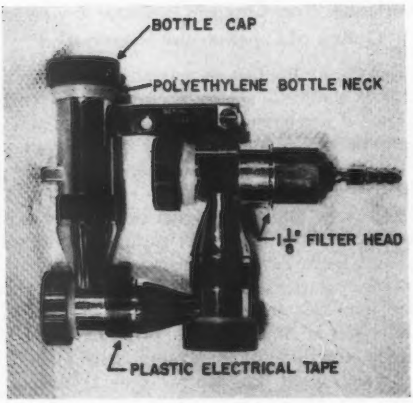

FIGURE 2. Modified Casella cascade impactor.

groups. The jet dimensions of several impactors from each group were measured and found to be the same. When sampling simultaneously from the same aerosol with impactors from each model group, the same mass distributions were obtained, indicating that in operation both models are equivalent.

The Casella-supplied press-on rubber caps at the tube ends, and rubber bands at the seams permit air leakage as brought out by the Air Cleaning Laboratory[16], Hyatt[9], and others. This leakage is eliminated in the modification shown in Figure 2. Polyethylene bottle necks (Two ounce wide-mouth bottle Catalog №1204 WM-HH, Palo Laboratory Supplies, 81 Reade St., New York 7, N.Y.) are bonded (Bonding Agent R-318, Carl H. Biggs Co., 11616 West Pico Boulevard, Los Angeles 64, California.) to the ends of the tubes and closed with screw caps eliminating air leakage at those points. (The two groups mentioned above suggested threaded metal caps and sleeves soldered to the tube for the same purpose.) Leakage at the seams is reduced with plastic electrical tape. A filter paper holder has been added as a fifth stage to collect any dust that passes through all four impaction stages. As pointed out by Laskin,[5, 6] this final stage is essential if the over-all size-mass distribution of an aerosol is to be determined. One other modification which was required for the calibration procedures, but which would not be required for field instruments, and is not shown in Figure 2, is an adaptor to permit connection of the impactor inlet to the sampling chamber.

Sampling With the Modified Casella Cascade Impactor: Glass microscope slides were used as the impaction stages in all runs. They were coated with a thin adhesive layer of Silicone 200 fluid applied in a benzene diluted solution with a glass stirring rod. The slides were air dried to evaporate the benzene solvent, and placed in the impactor. A Whatman №41 filter paper with a one-inch diameter filtering area was inserted as stage 5. Air was drawn through the impactor at a flow rate of 17.5 lpm.

Sampling Chamber and Associated Equipment: The sampling chamber (see Figure 3) was an inverted 20-liter polyethylene bottle with six sampling ports spaced equidistantly around its circumference. For each calibration run two samples were drawn through Casella impactors and two through membrane filters simultaneously. To obtain flow symmetry, air was drawn through all six ports at 17.5 lpm, the recommended flow rate for the Casella impactor. The major portion of the inlet air was drawn through a four-inch diameter Whatman №41 filter which removed background dust. When the valve was opened, a smaller amount of air flowed through an impinger containing the test dust. No attempt was made to generate a reproducible aerosol since the impactors were being calibrated against simultaneous and equivalent membrane filter samples.

Optical Sizing Procedure: All optical sizing was performed with 97x oil-immersion objective

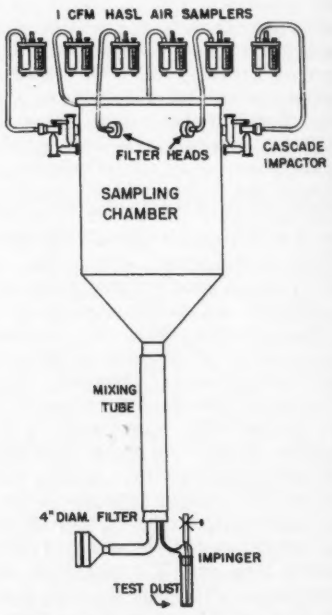

FIGURE 3. Sampling chamber and associated equipment.

using phase illumination. Phase illumination permits resolution of particles as small as 0.2 μ including those particles with an index of refraction close to the index of the immersion oil. In addition, it aids the discrimination between the test dust and extraneous contamination. The impactor slides were prepared for sizing by placing a drop of benzene diluted silicone over the dust deposit, followed by a cover glass over the silicone, and a drop of immersion oil on the cover glass. The membrane filter samples were prepared for optical sizing by placing a small wedge of the paper on a clean microscope slide; placing a drop of immersion oil of index of refraction of 1.507 on the filter to render it completely transparent, placing a cover glass over the filter; and a drop of immersion oil on the cover glass. (If the index of the oil is not exactly 1.507 a grainy background remains.)

The particles were sized with a Porton eyepiece graticule originally described by May.[1] A minimum of 200 particles in each sample were sized. On the impactor slides, at least two complete traverses were made across the dust deposit, in many cases necessitating the sizing of up to 1000 particles per sample.

Electron Microscope Sizing Procedure: Sections of membrane filters were transferred to electron microscope grids by the method of Fraser.[16] Electron micrographs were taken using a North American Philips Model EM-75 electron microscope.

Treatment of Size Distribution Data: The size distribution data were plotted on logarithmic probability paper. From the curves obtained, the mass median size on each stage was calculated using the formula developed by Hatch and Choate[17] cited previously. This formula states:

$$\log M_g' = \log M_g + 6.908 \log^2\sigma$$

where: M_g' = Mass median size = size at 50% intercept of mass distribution plot.

M_g = Median particle size = size at 50% intercept of particle distribution plot.

σ = Geometric standard deviation =

$$\frac{84.16\% \text{ size}}{50.00\% \text{ size}} = \frac{50.00\% \text{ size}}{15.84\% \text{ size}}$$

The particle distribution data from the optical and electron microscope sizing of the two membrane filter samples from each run were similarly plotted. From the curves of the membrane filter sizing, the mass median size of the over-all aerosol was calculated for each run. The mass distribution data from the chemical analysis of the impactor stages were plotted by the method of Laskin[5, 6] using the revised stage MMD values derived in this study, and the distributions obtained were compared with the membrane filter analyses.

Results

Representative particle size distribution curves obtained are illustrated in Figures 4 and 5. In all cases, it was possible to draw straight lines through the experimental points, indicating that the over-all aerosols generated, and the fractions collected on each stage, approached log normal distributions. For the stage calibrations, a minimum of six slides for each stage, for each dust, were sized and a single curve was drawn through all the points. Figure 4 shows the U_3O_8 stage calibration data. Each different symbol represents the data from a single calibration run for one of the impactors. Although the over-all size distribution and concentration of the aerosol were different in each run, the size distribution on a given stage was essentially constant. There was no consistent difference in the points from runs with larger or smaller over-all size distribution or with larger or smaller over-all dust loading. Also, there was no consistent difference between the points from the two impactors.

The median particle sizes and standard deviations found by the optical size analyses of stages 2, 3, and 4, for the various dusts, are tabulated in Table III along with the calculated MMD's. These MMD values are plotted against density in Figure 6. The slope of the lines is -2, verifying the theoretical relation that the mass median size on a stage varies inversely with the square root of the particle density. Figure 6 indicates that the MMD on stage 2 is equal to $19\rho^{-1/2}$ microns where ρ represents the particle density. Similarly, for stage 3, the MMD is $5.8\rho^{-1/2}$ microns, and for stage 4 the MMD is $1.7\rho^{-1/2}$ microns.

Simultaneous membrane filter samples were analyzed by optical microscope sizing for 10 of the calibration runs and by electron microscope sizing for 3 of those 10. The membrane filter particle size distribution curves, and the cascade impactor size-mass distribution curve obtained from one of these runs is shown in Figure 5. It can be seen that the electron microscope and optical sizing were in excellent agreement. Table IV lists the MMD's obtained by calculation from the optical and electron microscope particle size analyses of the membrane filters, and the corresponding MMD's determined for the same runs by chemical analysis of the cascade

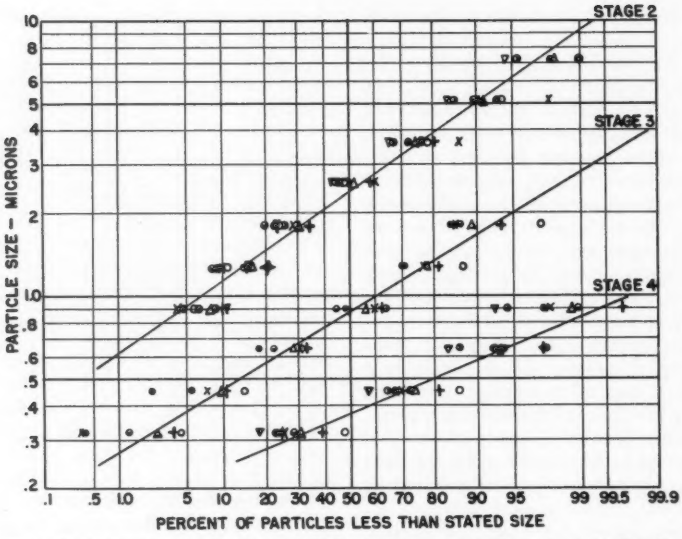

FIGURE 4. Particle size distribution of U_3O_8 dust on stages 2, 3, & 4 of Casella cascade impactors.

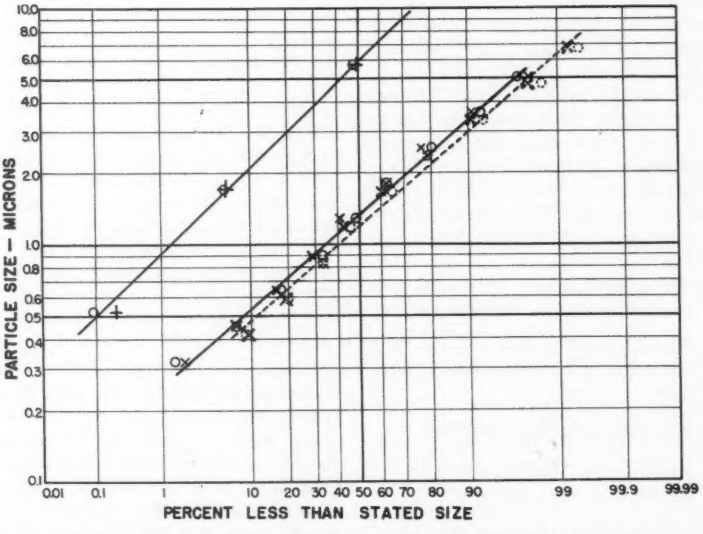

FIGURE 5. Particle size distribution of a UO_2 aerosol as determined by simultaneous membrane filters and Casella cascade impactors.

Upper solid curve: size-mass distribution from two cascade impactors.

Lower solid curve: particle size distribution from optical sizing of two membrane filters.

Broken line curve: particle size distribution from electron microscope sizing of the same two membrane filters.

TABLE III

Experimentally Determined Stage Size Distributions for Casella Cascade Impactors

Test material	Density[19] gm/cc	Stage 2			Stage 3			Stage 4		
		M_g	σ_g	M'_g	M_g	σ_g	M'_g	M_g	σ_g	M'_g
$(CH_3COO)_2 Cu \cdot H_2O$	1.9	2.36	2.12	13.0	1.41	1.75	3.6	0.69	1.52	1.16
SiO_2 (Quartz)	2.7	2.65	2.08	13.2	1.53	1.75	3.9	0.58	1.64	1.20
Fe (Powder)	7.9	2.50	1.79	6.9	1.32	1.51	2.2	0.53	1.38	0.72
U_3O_8	8.3	2.40	1.79	6.6	0.87	1.64	1.80	0.38	1.41	0.54
UO_2	10.9	2.67	1.68	5.9	1.27	1.43	1.87	0.38	1.37	0.51

M_g = median particle size—microns
σ_g = geometric standard deviation
M_g' = mass median size—microns

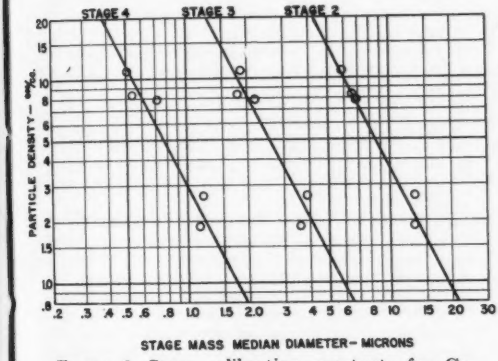

FIGURE 6. Stage calibration constants for Casella cascade impactors operated at a flow rate of 17.5 lpm.

TABLE IV

Comparison of MMD's from Cascade Impactor and Membrane Filter Analyses

Test number	Test material	MMD's from cascade impactor analyses	MMD's from membrane filter analyses	
			Optical microscope	Electron microscope
A	U_3O_8	18.0	18.6	—
B	U_3O_8	11.5	11.2	10.8
C	U_3O_8	5.0	7.3	—
D	U_3O_8	6.6	8.0	—
E	U_3O_8	6.2	5.8	—
F	U_3O_8	6.8	5.3	—
G	UO_2	5.9	7.0	—
H	UO_2	5.8	6.3	5.6
I	UO_2	5.9	6.2	—
J	UO_2	5.5	5.6	4.7

impactor stages. The agreement between methods appears to be very good.

After several experimental UO_2 runs, the inside walls of the impactors were washed down with toluene, and the washings were analyzed for uranium. In these runs, slide saturation was not reached, and the amount on the walls as compared to the amount on the collecting slide was in most cases less than 5%.

Summary and Conclusions

The estimation of the size distribution of an aerosol from the mass analysis of cascade impactor stages is a widely used technique having many advantages over other methods. Samples can be collected easily and analyzed with relatively little expense. The Casella cascade impactor is the only commercially available version, and the purpose of this investigation was to determine if it could provide useful and reproducible size analysis information. Its usefulness has been questioned since the various stage calibrations that had been proposed for it were not in agreement. With the same mass distribution data, each gave a distribution curve different from the others and different from the sizing of simultaneous membrane filter samples.

Other objections to the Casella cascade impactor which have been raised include: air leakage at the end caps and seams, poor collection efficiency for submicron particles, wall losses, and low collection capacity which limits sampling time to a few minutes. The HASL modification of the Casella cascade impactor reduced the air leakage with threaded end caps at the tube ends and tape at the seams. The addition of a filter paper stage after the impaction stages extended the collection efficiency to the submicron range. Wall losses were found to be negligible unless the impaction stages were overloaded. The stages become overloaded within minutes in many atmospheres, and this is a serious limitation which can only be overcome with moving impaction slides which continually

present a fresh impaction surface to the jet. A Casella cascade impactor fitted with moving stages has been described by May,[15] but this modification is not commercially available and would be difficult and expensive to fabricate.

A new calibration for the Casella cascade impactor, based on optical sizing of the impaction stages has been presented. The results obtained using this calibration have been found to check very closely with the results obtained from equivalent and simultaneous membrane filter samples. With the use of this new calibration, a Casella cascade impactor, modified to include a filter paper stage and to prevent air leakage, should be capable of providing a reasonably accurate estimate of the particle size distribution in the usual industrial atmosphere.

Acknowledgments

Grateful acknowledgement is hereby made to Emil E. Christofano of the Health and Safety Laboratory for assistance in the design of the experimental work; to Albert Berger who sized the impaction slides for the iron powder calibration; and to William B. Harris, Director, Environmental Sciences Division, Health and Safety Laboratory and Dr. K. R. May of Porton, England, for valuable editorial comment.

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Control of Potential Radiation Hazards at the Raleigh Reactor

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Introduction

THE FIRST Raleigh Reactor went critical in September 1953 and was operated successfully at North Carolina State College at power levels below and near 10 kw for approximately two years, during which time it was used in laboratory courses in the Nuclear Engineering curriculum and in basic nuclear research. This was the first reactor, outside of the A.E.C., to be operated on a college campus in a heavily populated area; and as such, the design specifications received very critical review by the North Carolina State College campus Health and Safety Committee as well as by the A.E.C. In May, 1955, small leaks developed in the wall of the stainless steel reactor vessel near the top of the core solution level. The radioactive liquid and gases were contained safely by the aluminum envelope surrounding the core and the reactor was shut down for repairs.[1] The leaks were detected shortly after they occurred, and before a hazard to personnel could develop, by the system described in this paper. The core vessel was sent to Oak Ridge National Laboratory for study where it was decided that the corrosion was caused by chlorides in the fuel solution. Because of the urgent need of continuing training of students, a simplified reactor was installed and put into operation in May, 1957. This was a homogeneous reactor, much like the first one, but designed to be operated at a lower power. This reactor is still being used, and is operated at power levels of 500 watts or less. Both of these reactors have been operated with the occurrence of very few detectable radiation exposures to personnel, no overexposures, and there has been no noticeable increase in radioactivity on the college campus. A new heterogeneous type reactor which will operate at about 10kw has been designed and it is planned that installation of this reactor will begin later this year.

Before the safety program is discussed, a review of the hazards encountered in the operation of the Raleigh Reactor is presented. Some of the situations presented are common to reactors of all types, but it should be borne in mind that this discussion is intended to apply to the present Raleigh Reactor. For the most part, the discussion is limited to routine unavoidable hazards; and only a brief outline of precautions applicable to the occurrence of a remote improbable accident is presented. However, it should be recognized that only by good administration and safety precautions which are adhered to continuously, can assurance be given that a reactor will be completely safe.

Potential Hazards

Radiation hazards associated with the reactor are of two types: (1) Those from external sources of radiation, and (2) those from radioisotopes that might become airborne or otherwise disposed so that they can enter the body. Hazards from external source are confined entirely to persons who are inside the reactor building. Radiation that leaks through the reactor shield, open beam holes, irradiated materials and radioactive waste disposal lines comprise the direct or external sources that exist during routine operations. These external sources are relatively easily protected against by employing shielding and/or distance between them and personnel, and by restricting the working time. This is borne out by the individual radiation exposure records of the Raleigh Reactor personnel. Since the first reactor went into operation, there have been no exposures in excess of the maximum permissible weekly dose of 300 mrem.[2] The maximum exposure was 240 mrem received by an individual in a two week period. This is about the amount of radiation that one might expect to receive from an ordinary chest x-ray. The average of all of the exposures from the reactor radiations received so far is not substantially greater than that expected from natural background radiation for the same period. It might be pointed out that it is not felt by any of the reactor staff that keeping radiation exposures down has hindered either the teaching or the research program.

Internal hazards are not so easy to protect against, and once a quantity of radioactive material has entered the body, it is usually very difficult to accurately determine the resultant

TABLE I

Comparison of Toxic Substances in Air

(Concentration in mg/m³)

Substance	Tolerance	Fatal dose
Chemical poisons		
Chlorine	2.9	290
Arsine	0.16	800
Beryllium	1.5×10^{-5}	?
Radioactive poisons		
U-233 (insol)	1690×10^{-9}	1690×10^{-5}
Pu-239	32×10^{-9}	32×10^{-5}
Sr-90	1.3×10^{-9}	1.3×10^{-5}

radiation dose. For this reason, and because the maximum permissible concentrations of radioisotopes in air and water are extremely small, rather extraordinary precautions that must be continuously maintained are required. A comparison between some chemical poisons and radioactive poisons has been made[3] (see Table I) in order to emphasize the special hazard due to radioactive materials.

As a general rule, radioactive poisons are more hazardous than chemical poisons by factors of about 10^6 to 10^9. Thus the containment problems, and the decontamination of effluent air and liquid waste are several orders of magnitude greater than they would be for the same quantities of chemical poisons.

There are four main sources at the Raleigh Reactor where there is potential for the release of radioactive material so as to present an internal hazard. They are: (1) The handling and processing of materials activated (i.e. radioisotopes produced) by the neutron flux in the reactor. Here, radioactive material may become airborne or may inadvertently be put into the liquid effluent drains connected to the sanitary sewer system. (2) The effluent gases released during normal operations. Since the Raleigh Reactor is of the homogeneous type, (in this case, a uranyl sulphate water solution) the radioisotopes of the gases krypton and xenon are always present in the air above the core solution. As air is purged across the core to remove the hydrogen gas that has been released from the water, it carries with it these radioactive gases. There is also the possibility of entrainment of other fission products. (3) At high power, the argon and dust particles in the air that surrounds the reactor can become significantly activated. (4) There always exists the probability that a leak will occur in the vessel that holds the reactor solution.

The probability that a major accident could occur in which the release of fission products would endanger the health of people outside of the reactor building is extremely remote. For one thing, the inventory of fission products is kept at a relatively low level so that even if an explosion took place in the reactor, it is unlikely that the area of severe contamination would extend very far beyond the reactor site. The excess reactivity is kept at a low enough value so that if, after the failure of a number of safety devices and if standard operating procedures were completely disregarded, the reactor went into an uncontrolled power excursion, it is doubtful whether the shield would be damaged. Again, very little activity would be expected to escape to areas beyond the reactor site.

It is important to note that the reactor is not located immediately on a drainage basin for any principal drinking water supply.

Restricted Areas

Figure 1 shows the general layout of the reactor building. The control room, reactor room, and all of the laboratories are regarded as restricted areas. These areas are enclosed by the dashed line in the figure. Entrances to these areas are restricted to persons who have been indoctrinated on safety rules and visitors who are accompanied by a reactor staff member. The wearing of film badges and pocket chambers is required by all persons who are in a restricted area. Monitoring equipment is provided at the control point in the Change Room where it is the responsibility of each person to check his clothing and person for contamination.

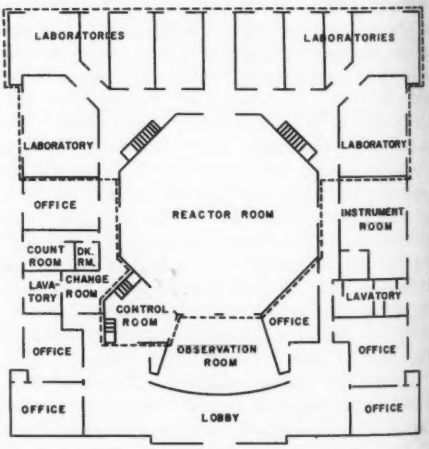

FIGURE 1. Layout of reactor building with restricted areas enclosed by dashed line.

The three access doors to the reactor room are normally locked to further restrict this area. These doors can be opened from the reactor room or they can be unlocked by actuating the solenoid locks from the control room.

The reactor assembly is on a lower level, about 12 feet below grade, which also contains utility and storage rooms, exhaust fans, and an air filter room.

Shielding

The reactor room has 12-inch thick masonry walls. Double paned windows with an eight-inch space between the panes are provided for viewing the reactor from an observation room. The space can be filled with water if extra shielding is required but this has never been found to be necessary.

The primary reactor shield is made of special high density (3.4gm/cc) concrete containing colemanite (1% boron by weight in finished concrete). The high density of this material improves the shielding properties against gamma rays and the boron serves to absorb the thermal neutrons. The minimum thickness of the shield is six feet. Beam holes are filled with stepped plugs made of the same materials when not in use. It has been found that this shield is quite adequate.

Ventilation System

The ventilation system for the restricted portions of the building employs air intake filters, an exhaust filter bed, exhaust fans, and a 100-foot stack for dispersing exhaust air into the atmosphere. It is always desirable to filter the air entering areas where contamination might occur because the dust particles can serve to enhance the spread of activity. The air flow patterns are arranged so that the air moves from the "cold" areas such as offices and hallways into the "hot" laboratories and reactor room where it is exhausted through ducts into the filter room. The two exhaust fans that pull the air through the filter bed handle 12,500 cfm each, and push the exhaust air up the stack. The top of the stack is at least 40 feet above the tops of the surrounding buildings. This extra elevation aids in the efficient dispersion of the gases. The filters are monitored frequently for radioactivity and it is interesting to note here that these filters collect substantial amounts of fallout following the testing of atomic bombs so that there is a considerable increase in the amount of analyzing that has to be done to determine the origin of the fission products. Activity in air filters taken from buildings as far as 20 miles from Raleigh have been studied for this purpose.

Radioactive Gas Disposal System

The hydrogen and oxygen generated by fission fragment bombardment of core water is removed from the air space in the core vessel by a continuous sweep of air across the core solution surface and exhausted into partially evacuated 55 gallon tanks. This serves to maintain the H_2-O_2 concentration well below explosive limits. Figure 2 is a schematic drawing of the gas disposal system. The air exhausted into this system contains the gaseous fission products, plus a certain amount of entrained solid materials. A condenser is provided to assist in trapping condensible materials. One or more vacuum barrels are exhausted to about 0.5 atmosphere pressure and serve as pumps or ballast for the entire system which is always held at a negative pressure relative to atmospheric. Thus the gases are drawn into the 55 gallon tanks where they are held for

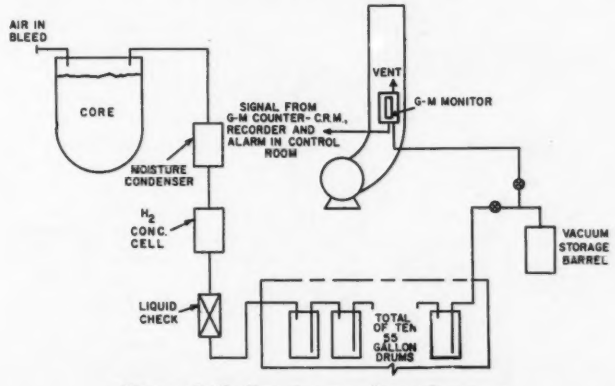

FIGURE 2. Radioactive gas disposal system.

radioactive decay. There are ten of these tanks connected in series at a depth of six feet below the surface of a water-filled pit located next to the stack. The water is used for shielding and to contain the accumulated daughter products of the fission gases in case a leak occurs in the system. The gases are finally released to the stack in a batch process. Measurements are made of the radioactivity in the vacuum barrel before each release to determine a release flow rate that will insure that the maximum permissible concentrations in air will not be exceeded.[4] Before the gases are diluted with air in the stack, they are passed through a chamber containing a thin-walled geiger counter. The output of this counter is fed into a count-rate meter which is attached to a recorder and alarm in the reactor control room. It is necessary to monitor these gases before the concentration is reduced in the stack because of the severe difficulties in counting the very low level that constitutes a maximum permissible concentration. A typical dilution factor of 1.5×10^6 is obtained in the following way: Gases are released at a rate of one cubic foot per hour into the stack stream which has a flow rate of 25,000 cubic feet per minute. Throughout the entire operation of the reactor, gases released through this system have not approached the maximum permissible concentrations. The usual rate of release is such that much less than one-tenth the maximum permissible amounts is allowed to leave the stack. A safe estimate is that the average concentration at the top of the stack is less than 1/1000 of MPC_a.

Sewage System

It is not intended that any quantity of radioactivity approaching maximum permissible concentrations as given by the A.E.C. Standards for Protection[4] shall be permitted to escape into the drain lines of the building. Short-lived radioactive materials are stored until sufficiently decayed, and long-lived materials are stored for disposal in other ways. Due to emergencies, accidental spillage or misoperation, above-tolerance concentrations of activity may on occasion escape into the drain lines. For this reason, therefore, no drain lines from the restricted areas of the building are connected to the campus sewer system, except through a radiation-monitored retention tank system. Figure 3 shows schematically the retention system for liquid wastes that may become contaminated. Three such tank systems are used. Normally, the bottom valve is closed and the center valve is open in the retention tanks placed between the drain lines and the sanitary sewer system. If the concentration of radioactivity in the half-full tank becomes higher than a predetermined value, a solenoid valve stops the flow into the sewer system and actuates an alarm in the control room. The remaining 250 gallon space in the tank then allows sufficient time for one to take corrective measures. An access tube permits periodic samples to be taken to check the validity of the continuous monitor located inside the tank.

Area Monitoring

A total of seven continuously recording ionization chamber type monitors are used to provide a record of the radiation levels at strategic points. Three of these are permanently mounted, two in the reactor room and one in the control room. Alarm circuits are included with these which will provide visible and audible signals in the control room in the event that radiation levels approach maximum permissible dose rates.

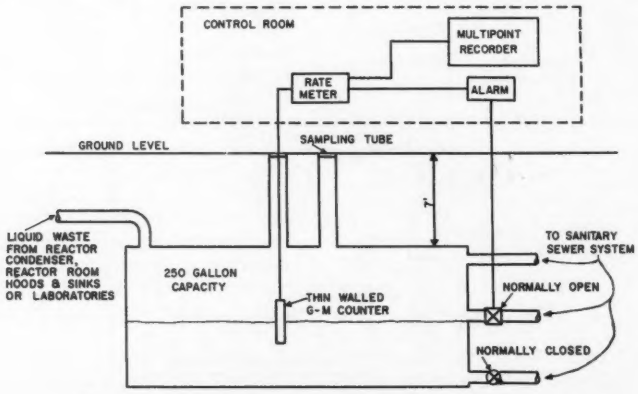

FIGURE 3. Retention system for reactor liquid waste.

TABLE II

Average Area Monitor Dose Rates

Station*	Long-term average mr/hr	Weekly average max. mr/hr	Weekly average min. mr/hr
Riddick	0.020	0.021	0.019
Withers	0.019	0.022	0.018
Broughton	0.019	0.021	0.017

* These stations are located approximately 200 yards from the reactor building, Riddick to the southeast, Withers to the northeast, and Broughton to the southwest. Prevailing winds are to the east.

These are checked before each reactor run for proper operation. Two other ion chambers are mounted on carts and are used to monitor various rooms in the reactor building. The remaining three are situated on the roofs of buildings near the reactor building. These last three were operated for several months prior to start-up to obtain background data for future comparisons. To date, all readings taken on these monitors reflect only normal background, except for the occasional higher readings that are observed following the atomic bomb tests. A summary of these readings is included in Table II. Figure 4 shows block diagrams of the various continuous automatic radiation ion chamber monitors and Figure 5 shows the details of a single unit. Not included in these figures are the thin window G-M monitors with audible signals that are in continuous operation at the personnel check-out point.

There are two other continuous monitors with alarms that are very important. These are the containment and shield-vent monitors. An aluminum containment envelope surrounds the reactor core vessel. Air flows out of this envelope through tubing to the ducts leading to the filter room. A containment monitor provided with shielding is incorporated in this line. Thus, if a leak occurs, it should be detected almost immediately.

The dust and argon in the air that fills the other spaces in the reactor shield can become activated. For this reason, the interior of the shield is kept at a very slight negative pressure with the air being exhausted through tubing to the filter ducts. A Shield Vent monitor is placed in this line to indicate the degree of activation and to provide a secondary alarm in the event of leaks.

In addition to the continuous monitors, frequent spot checking is done. Daily air filter samples are taken in the reactor room and from different locations on the campus. These are counted in a 2 π flow counter for both alpha and

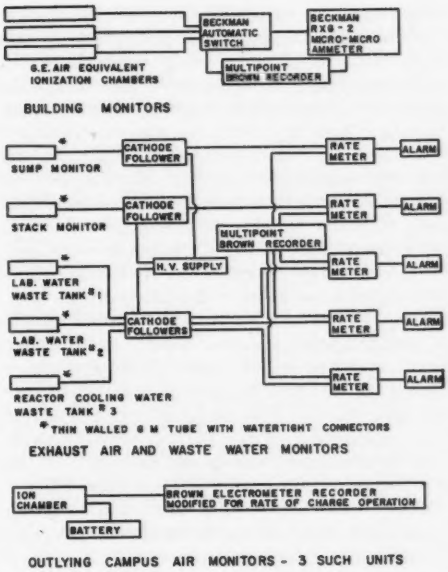

FIGURE 4. Continuous, automatic radiation monitors.

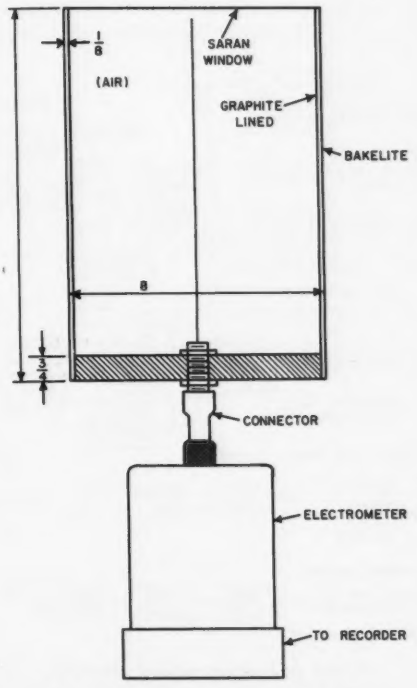

FIGURE 5. Ion chamber and amplifier.

beta. Work surfaces and floors in the reactor building are routinely smear-tested weekly and more often as situations may warrant. Water samples are taken from the waste retention tanks and from the water surrounding the gas storage barrels. These are generally one liter samples which are reduced in volume for counting in the well-type scintillation counter. Neutron surveys are made for both thermal and fast neutrons each time the reactor is operated with open beam ports. This survey work has been successful in preventing overexposure by calling attention to the areas where radiation levels are high. Early detection also helps to prevent the spread of contamination. In this regard, it has been found expedient to give the janitor specialized training in radiation hazards and the use of survey instruments. This specially trained janitor has incidentally proved to be very valuable since by checking his mops he frequently is the first to find contamination and by checking the ordinary waste cans he has on several occasions found sources of radioactive materials that were inadvertently deposited there.

Reactor Control Instrumentation

While it is not the purpose of this paper to discuss details that make a reactor intrinsically safe nor to discuss the mechanisms that control the operating power levels, it does seem appropriate to present a brief summary of those features of the control instrumentation that prevent the occurrence of a nuclear accident. These main features are shown in Figure 6, where each "TRIP" refers to a mechanism that can cause the safety rods to drop into the reactor and thus shut it down. A "trip" which "scrams" the reactor will occur if:

1. The power level exceeds a pre-set value
2. The difference in power level as indicated by two identical channels becomes greater than 40%
3. The rate at which power is increasing becomes too great (The Raleigh Reactor control instrumentation is so constructed that a "scram" will be initiated if the period becomes less than five seconds. Period is defined as the time required for the power level to increase by a factor of e, the base of the natural logarithms.)
4. The gamma ray dose rate at a fixed position in the reactor shield exceeds a pre-set level.
5. An electrical power failure, or large power surge occurs.
6. The hydrogen concentration exceeds 3% in the air above the core solution.
7. The manual "scram" button on the control panel is depressed.
8. The voltage drops below a pre-set value on either of the chambers used to supply power level information.

This entire system is checked for proper operation before each start-up of the reactor.

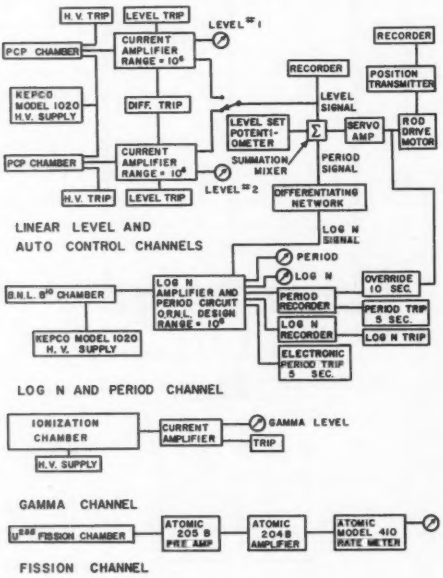

FIGURE 6. Reactor control channels.

Administration and Procedures

The plans for each new experimental use of the reactor are reviewed by the Campus Safety and Health Committee which is appointed by the Chancellor. Their approval must be obtained before the experiment is performed. It has been found that a safety officer or health physicist who is working for the people responsible for the experiments with the reactor or isotopes can have his judgement regarding safety somewhat biased. In fact, if his immediate supervisor desires to disregard certain precautions, it has been found that compromises, not always in the best interests of safety, will be made. For this reason, the Campus Safety and Health Committee operates independently of any single department and hires a campus Radiological Safety Officer who is responsible only to the Committee and the Chancellor. The Campus Radiological Safety Officer is kept informed of all reactor operations. He recommends safety procedures and has the power to demand cessation of any activity that

he does not regard as being safe. He also carries out a monitoring program that is independent of the one carried out by the reactor personnel.

In addition to the reviews made by the Campus Safety and Health Committee, each proposed operation involving the reactor facilities is studied by the Director of the Reactor Project and by the Reactor Health Physicist. They determine the detailed procedures and equipment required to insure safety. Some of the important factors that are studied in each case are: (1) the possibility that a change in reactivity can occur by introducing substances into or close to the reactor, (2) the possibility that a corrosive material can become unconfined within the reactor assembly, (3) the possibility that pressure will build up in a closed container due to the action of heat or radiation or a material being irradiated, (4) the possibility that the physical form of a material being irradiated will be changed so as to create unusual hazards upon removal from the reactor, (5) the degree of exposures that can be expected because of open beam ports, experimental arrangements or activated materials being removed, (6) the precautions necessary to take care of the evolution of hydrogen gas and radioactive gases, (7) radioactive waste disposal problems that may occur, and (8) additional shielding that may be required.

Two important requirements of the safety procedures are that a person does not work alone in radiation areas, and in all operations where radioactive materials are being transferred from the reactor, one person is present whose sole responsibility is safety.

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A Survey of Radiation Received by Dentists and Dental Assistants*

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FOR THE past nine years, (1950–1958) a program for determining the exposure received by persons engaged in dental radiography has been conducted using film monitoring badges and ionization survey meters. Film badges have been worn on the lapel of the uniform or in a shirt pocket. In this manner all reportable exposures are at the same relative level above the floor and show what is believed to be as close to a significant total body figure as is possible to obtain with this method of monitoring.

Films have been processed and evaluated as outlined in previous articles by Cowing, Spalding, and DeAmicis.[1, 2, 3] Control films have been irradiated to known intensities of 60, 70, and 80 Kv x-rays having approximately the same effective wavelengths as those produced by the average dental x-ray unit. Curves of net density vs. roentgens drawn from data gained from these control films was used for evaluating the density of the exposed badges. All measurements and standardizations were done using a Victoreen condenser type r-meter.

For the period of this study 3,134 films have been worn by technicians and dentists in 233 offices and three clinics where from 5 to 400 exposures per week were made. Badges were worn for two-week intervals, findings have been interpreted in terms of weekly exposure by dividing the actual dose received by two.

Figure 1 shows the relationship of exposures received by personnel expressed both numerically and in terms of percentage of total films worn.

From this compilation of data the incidence of exposure from 0 mr to 9 mr remained relatively low over the years. The exposures in the 10 mr to 99 mr range for all years approached 50 per cent of the persons monitored. Exposures from 100 mr to 199 mr remained close to 20 per cent of the total monitored while the 200 to 299 mr range was found to be consistently close to 10 per cent of the total. Those receiving over 300 mr, or over the tolerance as established by the National Committee on Radiation Protection fluctuated, but not significantly, from the three per cent reported by Moeller, *et al.*[4]

In attempting to learn the reasons for the exposures above 200 mr, it was found that in all cases the work load for a particular technician was the factor which most significantly influenced the exposure. When patients were waiting to be radiographed or when the dentist was waiting to work on a patient who was to be radiographed by his technician, especially in clinics, pressure caused the technician to become careless and take "short cuts" that resulted in exposure to herself.

A comparison by Spalding *et al.*[5] of the exposure received by radiologists and other physicians using x-rays in their practice shows that the exposure to dentists and dental assistants is third among physicians using x-rays in their practice. Urologists and neurosurgeons receive more radiation than dentists while conducting their routine procedures. Radiologists are seventh preceded by those mentioned plus orthopedic surgeons, gynecologists, and thoracic surgeons.

Gorson *et al.*[6] have a comprehensive report of exposures in several dental offices. Many articles in the literature show the exposure to the patient and describe methods of reducing this exposure by utilization of faster film, filters, and longer cones.[7, 8, 9, 10]

Richards *et al.*[11] point out the problem of personnel exposure and stress the recommendation of the National Committee on Radiation Protection for a reduction in the permissible tolerance dose to 0.1 roentgens per week from the present 0.3 roentgens per week. Spear[12] reports that a survey of 20 general practitioners in dentistry in Indianapolis showed an average of 2,772 exposures per year are made with the patient averaging from 2 to 13 exposures each.

Todd and Worth[13] report after a survey of 23 dental offices in Kentucky that the typical exposure rate to dental workers was 12 mr per minute of x-ray on time and that this dose could be reduced by a factor of two by adding 1.6 mm of aluminum to the tube as a filter.

* This work was done under U. S. Atomic Energy Commission Contracts AT(30-1) -609 and AT(30-1) -901 with the New England Deaconess Hospital.

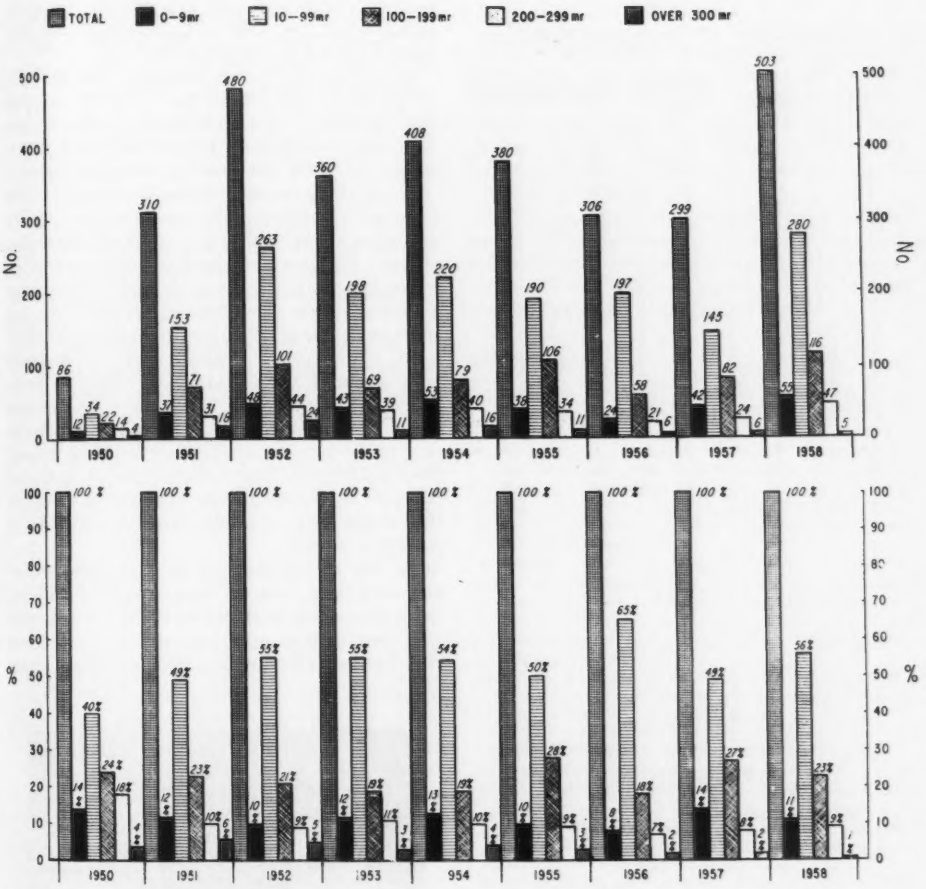

FIGURE 1. Number of badges exposed to designated dosage and percent of total badges worn in each dose group.

Moeller *et al.*[4] report from a survey conducted that three per cent of the exposures exceeded 0.3 roentgens per week and that the operators of dental x-ray machines receive approximately 0.1 roentgens of total body radiation per eight mouth examinations of 14 exposures each.

To verify surveys reported by other investigators and attempt to find a reason for the high exposure rates reported, films were placed on personnel working with 23 separate x-ray machines. No attempt was made to instruct the worker in technique or their position in relation to the x-ray unit. Many of the units had no added filtration and most were not properly diaphragmed to limit the beam to a reasonable size. From data collected under these conditions, Table I has been compiled to show the average milliroentgens per exposure and the total exposure rate for the person operating the machine. In each case one technician or dentist took all the exposures on the particular machine—the badge being worn only while the technician was working with the designated machine.

After a review of the outcome of the survey, a visit to each installation with recommendations as to the position of operator and added filtration and diaphragming was undertaken and again the survey was conducted in exactly the same manner. Table II shows the total dose per week and dose per exposure received by the operator after the second survey. In all cases there was an appreciable decrease in exposure after the opera-

TABLE I

X-ray Exposures of Uninstructed Operators

Machine	X-ray operating time (sec/week)	Number of exposures	mr/week	mr/exposure
A	186	65	135	2.1
B	209	98	200	2.0
C*	111	84	240	2.8
D	236	81	25	.31
E	79	39	40	1.0
F	88	29	109	3.8
G	165	92	85	.92
H	150	86	50	.58
I*	65	70	35	.5
J	130	69	120	1.7
K	140	47	85	1.8
L	111	49	60	1.2
M	365	158	210	1.3
N	210	99	300	3.0
O	265	125	145	1.15
P	130	59	260	4.4
Q*	56	71	25	.35
R	100	80	150	1.9
S	93	36	210	5.8
T	530	199	700	3.5
U	405	140	535	3.8
V	316	135	600	4.5
W	726	340	420	1.2

* Indicates high-speed film used.

TABLE II

X-ray Exposures of Operators after Special Safety Instruction

Machine	X-ray operating time (sec/week)	Number of exposures	mr/week	mr/exposures
A	145	58	25	.42
B	193	92	22	.26
C*	109	80	21	.27
D	220	74	24	.33
E	76	38	11	.29
F	101	36	23	.65
G	164	90	32	.36
H	143	82	39	.48
I*	58	63	19	.30
J	125	66	27	.41
K	136	44	16	.37
L	120	58	26	.46
M	300	125	43	.34
N	230	106	44	.41
O	245	110	45	.41
P	130	59	18	.30
Q*	51	67	24	.36
R	94	75	35	.47
S	88	34	18	.54
T	485	186	410	2.2
U	426	143	145	1.01
V	389	152	260	1.7
W	601	209	105	.5

* Indicates high-speed film used.

tor understood how and why she was being exposed, where the zone of highest radiation was, and how to efficiently avoid that area.

In all installations the operator was instructed to get as far away from the x-ray unit as possible, preferably outside the room. Most rooms were small, averaging 6 feet wide and 8 feet long, which did not provide the possibility of utilizing distance as a protection media. If it were not possible for the operator to leave the room, or stand behind a suitable barrier, then she was instructed to stand so that it would be impossible for her to be in the zone of scattered radiation of less than 120 degrees from the primary and at least three feet from the tube head.

All of the dentists taking part in this study were asked if it were necessary that the technician be in the room when the exposure was made. It was agreed that it was not necessary, and all were more than cooperative in having their timer cords lengthened or relocated so that it would be possible for the operator of the x-ray unit to get away from the source of radiation or behind a barrier.

As part of the program to better understand the originally noticed high exposure rate of dental personnel as shown in Table I, a phantom and dental x-ray unit were set up to simulate the patient (Figure 2). Measurements were

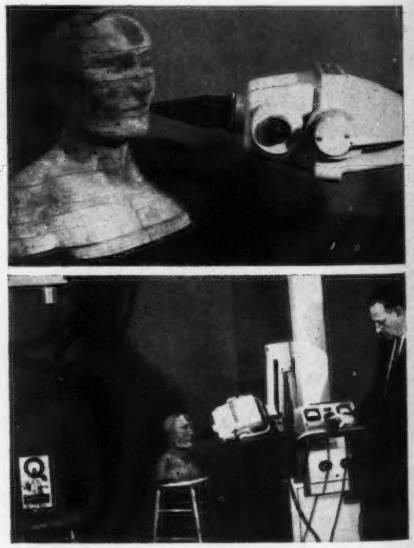

FIGURE 2. Method of measuring radiation intensity about the X-ray unit using a phantom as the patient.

made about the phantom to determine if the previous idea of standing directly behind the tube was the best or if the newer concepts of standing to the side of the unit was safest. From measurements taken using an ionization-type survey meter it was learned that the number of variables involved causing the scattered radiation made each diagnostic setup an entity unto itself, and no definite statement could be made as to where the best place to stand would be. Rather, it was found that for a given location the following factors influenced the dose at that locus:

1. The angle of the primary beam,
2. The density of the part from which the radiation was scattered,
3. The level above the floor where measurements were made,
4. The filtration both inherent and added in the x-ray unit,
5. The coning of the x-ray beam and field size, and
6. The number of obstacles in the room which would act as second scatterers.

Because of these variables, there was no justification to relax the conclusion that the only safe place was outside the room.

While the measurements were made with the phantom it was observed that when an ionization meter shows that a definite area is free from radiation under set circumstances of machine and patient position, it may not be the case when any of the above factors are changed. Because of this, the most practical means of monitoring personnel is with an ionization chamber or film badge attached to the person to be monitored. The location at which this indicating device is placed depends upon what is wished to be learned and how accurately the information gained from what the device sees in its relatively small crosssection area can be interpreted in terms of total body radiation.

Conclusions

1. Dental personnel receive more x-ray during their normal routine than do most others who utilize radiation for diagnostic techniques.
2. With the proper education and evaluation of the physical hazards connected with dental x-ray machines, exposures to operators can be appreciably reduced.
3. The interpretation of film badge readings and results of surveys conducted with ionization-type survey meters must be carefully evaluated to be of value when transposing their information into total-body exposure figures.

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Industrial Hygiene

Definition, Scope, Function and Organization

This statement was prepared by an Ad Hoc Committee composed of Jack C. Radcliffe, Chairman, George D. Clayton, William G. Fredrick, Kenneth W. Nelson and Elmer P. Wheeler, and has been approved by the Officers and Board of Directors of the American Industrial Hygiene Association.

Industrial Hygiene

Industrial Hygiene is that science and art devoted to the recognition, evaluation and control of those environmental factors or stresses, arising in or from the work place, which may cause sickness, impaired health and well being, or significant discomfort and inefficiency among workers or among the citizens of the community.

Industrial Hygienist

An Industrial Hygienist is a person having a college or university degree or degrees in engineering, chemistry, physics, or medicine or related biological sciences who, by virtue of special studies and training, has acquired competence in Industrial Hygiene. Such special studies and training must have been sufficient in all of the above cognate sciences to provide the abilities: (1) to recognize the environmental factors and stresses associated with work and work operations and to understand their effect on man and his well being; (2) to evaluate, on the basis of experience and with the aid of quantitative measurement techniques, the magnitude of these stresses in terms of ability to impair man's health and well being; and (3) to prescribe methods to eliminate, control or reduce such stresses when necessary to alleviate their effects.

Scope of Industrial Hygiene

Industrial Hygiene primarily involves: (1) the recognition of environmental factors and stresses associated with work and work operations, and the understanding of their effects on man and his well being in the work place and the community; (2) the evaluation, through training and experience, and with the aid of quantitative measurement techniques, of the magnitude of these factors and stresses in terms of ability to impair man's health and well being; and (3) the prescription of methods to control or reduce such factors and stresses when necessary to alleviate their effects.

Recognition of environmental factors and stresses which influence health requires a familiarity with work operations and processes. The categories of stresses most frequently of interest are: (1) chemical, in the form of liquid, dust, fume, mist, vapor or gas; (2) physical energy, such as electromagnetic and ionizing radiations, noise and vibration and extremes of temperature and pressure; (3) biological, such as insects and mites, molds, yeasts and fungi, bacteria, and viruses; (4) ergonomic, such as body position in relation to task, monotony, boredom, repetitive motion, worry, work pressure and fatigue. The effect of these four areas of stress on man's health and well being must be recognized. It is important to know whether such stresses are immediately dangerous to life and health, whether they produce an acceleration of the aging process or whether they will cause only significant discomfort and inefficiency.

Evaluation of the magnitude of the environmental factors or stresses arising in or from the work place is essential in order to predict the probable effect on health and well being. The Industrial Hygienist, by virtue of training and experience, and aided by quantitative measurement of the chemical, physical energy, biological or ergonomic stresses can render an expert opinion as to the healthfulness of the environment, either for short periods or for a lifetime of exposure.

Prescription of corrective procedures, when necessary to protect health, is based on past experience, knowledge and the quantitative data available. Among control measures most frequently used are: (1) isolation of a process or work operation to reduce the number of persons exposed; (2) substitution of a less harmful material for one which is more dangerous to health; (3) alteration of a process to minimize human contact; (4) ventilation and air cleaning to provide an atmosphere safe for human occupancy; (5) reduction of exposure to radiant energy by shielding, increasing distance and limiting time; (6) wet methods to reduce emission of dust to the atmosphere such as in mining and quarrying; (7) good housekeeping, including cleanliness of the work place, proper waste disposal, adequate washing, toilet and restroom facilities, healthful drinking water and eating facilities, and control of insects and rodents; (8) personal protective

devices, such as special clothing and eye and respiratory protective equipment.

The terms worker, workplace and community, as used in this discussion, are hereby defined: A worker is a person engaged in any occupation or vocation. A workplace is any building, structure, excavation, site, device or area in which work is done. A community is the environs of one or more workplaces.

Function of the Industrial Hygienist

Within his sphere of responsibility, the Industrial Hygienist will:

1. Direct the Industrial Hygiene program.
2. Examine the work environment and environs:
   a. Study work operations and processes and obtain full details of the nature of the work, materials and equipment used, products and byproducts, number and sex of employees, and hours of work.
   b. Make appropriate measurements to determine the magnitude of exposure or nuisance to workers and the public. In doing so, he will:
      (1) select or devise methods and instruments suitable for such measurements;
      (2) personally or through others under his direct supervision conduct such measurements; and
      (3) study and test material associated with the work operation.
   c. Study and test biological materials, such as blood and urine, by chemical and physical means, when such examination will aid in determining the extent of exposure.
3. Interpret results of the examination of the work environment and environs in terms of ability to impair health, nature of health impairment, workers' efficiency and community nuisance and/or damage, and present specific conclusions to appropriate interested parties such as management and health officials.
4. Make specific decisions as to the need for, or effectiveness of, control measures, and when necessary, advise as to the procedures which will be suitable and effective for both the environment and environs.
5. Prepare rules, regulations, standards and procedures for the healthful conduct of work and the prevention of nuisance in the community.
6. Present expert testimony before courts of law, hearing boards, workmen's compensation commissions, regulatory agencies and legally appointed investigative bodies covering all matters pertaining to Industrial Hygiene as described in this document.
7. Prepare appropriate text for labels and precautionary information for materials and products to be used by workers and the public.
8. Conduct programs for the education of workers and the public in the prevention of occupational disease and community nuisance.
9. Conduct epidemiologic studies among workers and industries to discover possibilities of the presence of occupational disease, and establish or improve threshold limit values or standards as guides for the maintenance of health and efficiency.
10. Conduct research to advance knowledge concerning the effects of occupation upon health and means of preventing occupational health impairment, community air pollution, noise, nuisance and related problems.

Organization of Industrial Hygiene Activity

By definition, the field of Industrial Hygiene utilizes several essential basic disciplines. For this reason, a practitioner in any one of these basic disciplines may look upon Industrial Hygiene as a part of his field. The physicist may see Industrial Hygiene as part of his domain when the protection of the worker from ionizing radiation and noise are of concern. The chemist, recognizing that the practice of Industrial Hygiene includes the use of analytical chemistry techniques, may feel that Industrial Hygiene is a part of the broad field of chemistry. The engineer may regard Industrial Hygiene to be within the scope of engineering because of the various engineering control techniques utilized. The physician, concerned with the treatment of industrial workers, may consider Industrial Hygiene a part of industrial medicine because one of its aims is to prevent disease. Actually Industrial Hygiene is a profession in its own right.

Uncertainties and questions exist as to where Industrial Hygiene activities should be assigned within corporate structures. In public corporations, Industrial Hygiene might appear to be a proper activity within the Department of Labor, which is concerned with those who work; or the Department of Health, which is concerned with the health of all the people. In Health Department organizations, where most governmental Industrial Hygiene activities are centered, each traditional division such as Adult Health, Preventable Diseases, Laboratories, Environmental Sanitation, etc., may feel that Industrial Hygiene is logically a part of its operation. Actually, In-

dustrial Hygiene functions best as an independent division of equal stature. In private corporate structure, Industrial Hygiene might appear logically to be a function of the Personnel, Research, Process Control, Engineering or Medical Departments. However, Industrial Hygiene, because it has aspects and implications concerning legal, medical, engineering, purchasing, sales, workmen's compensation, public and labor relations, best functions as a discrete organization responsible to top management levels.

Many corporations initiate programs in Industrial Hygiene by hiring one man with broad experience and knowledge. From such a nucleus there should develop an effective Industrial Hygiene organization which would include the director, well trained and certified in Industrial Hygiene, and such supporting field and laboratory personnel as may be required.

Every Industrial Hygienist has special proficiency in at least one essential basic discipline, such as engineering, chemistry, physics, medicine, toxicology, or biological science, and has broad knowledge concerning the recognition, evaluation and control of stresses in the work environment likely to impair health. However, best results are obtained if the staff includes Industrial Hygienists drawn from several of the basic sciences. The impact of such a team approach provides the best protection to health of workers from environmental stresses.

The team may be supplemented by specialists not trained in Industrial Hygiene. Such specialists may be chemists proficient in trace analysis, physicists expert in ionizing radiation or acoustics, industrial toxicologists, bacteriologists, ventilation engineers, sanitary engineers and physicians.

HYGIENIC GUIDE SERIES

Parathion*

O,O-Diethyl O-p-nitrophenyl thiophosphate

I. Hygienic Standards

A. RECOMMENDED MAXIMUM ATMOSPHERIC CONCENTRATION (8 hours): 0.1 milligram of parathion per cubic meter of air (mg/m³).[1]

1. *Basis for recommendation:* Animal studies and human experience. Exposure to 0.1–0.8 mg/m³ in processing plant showed slight but significant lowering of cholinesterase activity while 2–15 mg/m³ over a period of 2–5 days depressed cholinesterase activity 25%. Recommended atmospheric concentration 1/10 of value required to produce biochemical response but no symptoms in man.[2]

B. SEVERITY OF HAZARDS:

1. *Health:* High, especially for acute and subacute exposures. May enter body through inhalation of dust or spray mist and by ingestion, but greatest number of occupational poisonings occur as a result of absorption through the intact skin. Because of the low vapor pressure, inhalation in this form is negligible at ordinary temperatures. Parathion inactivates cholinesterase enzyme in the central nervous system and produces symptoms similar to those from chemical warfare agents known as "nerve gases" or "nerve poisons" to which parathion is related chemically and pharmacologically. Earliest symptoms occur within 0.1–5 hours or more following acute exposure. They include unsteadiness, blurred vision, feeling of tightness in chest, nausea, general weakness and difficulty in breathing. Absorption of parathion produces paranitrophenol in urine. Present *Food and Drug Administration* tolerance for residual parathion on foodstuffs is one ppm although later studies indicate that up to three ppm parathion in total diet does not depress blood cholinesterase.[4] Female rats are markedly more susceptible to parathion than males,[5] but this difference has not been confirmed in nonrodents.

2. *Fire:* Negligible.

C. SHORT EXPOSURE TOLERANCE: Minimum lethal dose by ingestion is not certain and has been variously estimated as from less than 10 to 20 mg and 100 mg/kg.[6] based on early technical grade products. Animal studies indicate parathion is very nearly as toxic when administered to the skin as by the oral route.

D. ATMOSPHERIC CONCENTRATION IMMEDIATELY HAZARDOUS TO LIFE: Short exposure tolerance by inhalation has not been determined, but parathion's rapid penetration of all body tissues makes it unlikely that acute exposure dosages are less than those for other modes of entry cited above.

II. Significant Properties

Parathion is a brown or yellowish liquid often possessing a characteristic odor. Technical grade contains 95% parathion.

Chemical formula:	$(C_2H_5O)_2PSOC_6H_4 \cdot NO_2$
Molecular weight:	291.3
Specific gravity:	1.25 (25°C/4°C)
Boiling point:	157–162°C
Relative vapor density:	10 (air = 1)
Vapor pressure:	0.00003 mm of Hg at 24°C
Solubility:	Very slightly soluble in water (20 ppm), soluble in many organic solvents in-

* The Committee wishes to acknowledge the valuable assistance of Dr. Boyd Shaffer and Dr. Wayland Hayes in the preparation of this Guide.

cluding esters, alcohols, ketones, ethers and aromatic hydrocarbons.

III. Industrial Hygiene Practice

A. RECOGNITION: Used in agriculture for control of insects. Sprayed as 1–4% parathion in water by airplane or tractor-drawn ground equipment in large-scale applications; by other methods inside greenhouses and to small outside areas. Also supplied as 25% water-wettable dust. Inhalation of spray in confined areas such as greenhouses may be a hazard for several hours after application. Residual parathion on plants may be transferred through skin contact although the possibility of severe poisoning from this source appears slight.[7, 8]

B. EVALUATION OF EXPOSURE:

1. *Direct instrumentation:* None
2. *Chemical method:* Collection in impinger containing isopropyl alcohol. Samples can be analyzed by the A.C.G.I.H. approved method.[9] Nitro group in molecule reduced to an amino group by treatment with zinc and HCl and changed to diazonium salt by treatment with $NaNO_2$. A colored complex is formed with the addition of n-(1-naphthyl) ethylene diamine dihydrochloride and read in a photometer at 540–550 $m\mu$.

C. RECOMMENDED CONTROL PROCEDURES: Maintain atmospheric concentration below 0.1 mg/m³. Avoid physical contact with parathion or materials to which parathion has been applied by use of impervious protective clothing including respirator approved for protection against organic phosphates, cap or hat, coveralls, rubber gloves and boots. Provide clothing changes and shower facilities for use following contamination and at conclusion of work period. Wherever parathion is handled, an emergency supply of atropine should be on hand and available for immediate emergency use.

IV. Specific Procedures

A. FIRST AID: If symptoms include blurred vision, abdominal cramps and tightness in the chest, do not wait for a doctor but give two atropine tablets (each 1/100 grain) at once. It is preferable to allow the tablets to dissolve under the tongue. This treatment may be repeated in one-half hour if the doctor does not arrive earlier. Exposure should be terminated as rapidly as possible by removal to an uncontaminated area, removal of clothing and thorough cleansing of the skin with warm water and soap. Artificial respiration may be needed to counteract breathing difficulty.

B. SPECIAL MEDICAL PROCEDURES:

1. *Tests for absorption:* Lowering of cholinesterase level, especially in blood red cells is a definite indication of parathion absorption. Symptoms may or may not appear even when cholinesterase is reduced to 30% of normal.[10] Recovery rate may be estimated by degree of reappearance of cholinesterase in the blood.
2. *Treatment:* Parathion poisoning is a grave medical emergency. Unless exposure has been overwhelming, patients may be saved by prompt treatment with relatively large doses of atropine. Administration of 1/25 grain (2.5 mg) intravenously at 15-minute intervals for a total of three or more doses may be required. This may be followed by intramuscular administration of 1/50 grain at somewhat longer intervals to maintain full atropinization. Severe cases may require as much as 20–30 mg in the first 24 hours. A mild degree of atropinization should be maintained for at least 48 hours.[11, 12] The use of newer antidotes, such as 2-PAM, appears to be promising when used in conjunction with atropine. The physician should refer to current literature for such information. During period of recovery from parathion poisoning, further exposure to any cholinesterase inhibiting substance should be avoided as effects are cumulative.

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DDT*

2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane

I. Hygienic Standards

A. Recommended maximum atmospheric concentration (8 hours): One milligram DDT per cubic meter of air (mg/m³).[1]
   1. *Basis for recommendation:* Animal studies and human experience.[2]

B. Severity of hazards:
   1. *Health:* Moderate for repeated inhalation exposures; low for acute inhalation, ingestion and absorption through the skin. Heavy exposure to DDT dust may result in eye and skin irritation, chiefly mechanical. Absorption produces high bis-p-chlorophenyl acetic acid (DDA) levels in urine.[3] Ingestion of approximately one gram of DDT per day in adults probably required to produce significant chronic cumulative poisoning. Present standard for residual DDT on foodstuffs is 7 ppm.[4] When deaths have occurred following ingestion of solutions, symptoms have been characteristic of the solvents, such as kerosene, in which DDT was dissolved. DDT affects the central nervous system and may produce liver damage following chronic exposure.
   2. *Fire:* None.

C. Short exposure tolerance: Minimum lethal dose for adults by ingestion has been variously estimated at 10–20 grams DDT in oil and from 200–500 milligrams per kilogram of body weight. Short exposure tolerance by inhalation not known.

D. Atmospheric concentration immediately hazardous to life: Unknown and probably unobtainable.

II. Significant Properties

DDT is a white needle-shaped crystalline solid. The "para-para" compound is the active ingredient but the less active "ortho-para" compound occurs as a major impurity in the technical product.[5]

Chemical formula:	$CCl_3CH(C_6H_4Cl)_2$
Molecular weight:	354.5
Specific gravity:	0.98–0.99
Boiling point:	Melts at 107°C, decomposes before reaching boiling point
Solubility:	Insoluble in water; soluble in alcohol, benzol, ether, petroleum solvents, carbon tetrachloride.

III. Industrial Hygiene Practice

A. Recognition: Widely used in agriculture and public health for control of insects. Largest consumption of all organic pesticides. Frequently sold to the consumer in the form of a 10% mixture with an inert mineral dust such as talc or as a 5% solution in kerosene. Large-scale crop dusting and mosquito-control applications by aircraft; smaller areas by conventional methods. Workers exposed to DDT in insecticide manufacturing plants.

* The Committee wishes to acknowledge the valuable assistance of Dr. Wayland Hayes in the preparation of this Guide.

The exposures of occupational significance are inhalation of dust or mist. Prolonged skin contact with oil solutions may produce dermatitis and possibly excessive absorption.

B. EVALUATION OF EXPOSURE:
1. *Direct instrumentation:* None.
2. *Chemical method:* Collect with standard impinger in isopropyl alcohol. Convert to inorganic chlorides by hydrolysis with KOH, or by burning, and titrate chlorides with silver nitrate.[5]

C. RECOMMENDED CONTROL MEASURES: Maintain workroom atmosphere below 1 mg/m³ by process enclosure and/or exhaust ventilation. Prevent skin contact by the use of protective clothing and chemical-type goggles; provide facilities which permit good personal hygiene.

IV. Specific Procedures

A. FIRST AID: Rarely required for occupational exposures. If DDT has been dissolved in a toxic solvent, poisoning from the specific solvent may occur. For acute exposure by ingestion, induce vomiting and administer general supportive first aid treatment.

B. SPECIAL MEDICAL PROCEDURES: None for preplacement. Excretion of DDA in urine has been suggested as a quantitative estimate of DDT absorption and storage.[3, 6]

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Thorium and Its Compounds

I. Hygienic Standards

A. RECOMMENDED MAXIMUM ATMOSPHERIC CONCENTRATION (40 hours): (for Thorium^{232} in equilibrium with Thorium^{228})

Authority	*μc/cc**	*μg/m³*
ICRP[14]	9×10^{-11}	400
NCRP[16]	3×10^{-11}	130
10 CFR Part 20[8]	5×10^{-11}	110
Proposed 10 CFR Part 20 (Revised)	9×10^{-11}	200

* Based on calculated radiation dosage to lungs or bone as critical organs and on comparison with uranium.[14]

† Although both authorities state the MAC in terms of μc/ml, ICRP and NCRP use 4.4×10^{12} d/m/curie while 10 CFR Part 20 uses 2.2×10^{12}. The MAC may be converted to micrograms of thorium per cubic meter of air by using 1 d/m = 1 μg.

Certain recent animal toxicity data indicate radiation dosage from thorium might better be compared to that of plutonium than to uranium.[2, 11] Calculations based on these and other animal data suggest that permissible occupational exposure to thorium should be reduced to 2×10^{-12} μc/cc for 40 hrs/wk.[16] However, the most recent review on the subject strongly supports the uranium comparison and retention of the present limits.[12] The NCRP has recognized this disparity and has proposed 3×10^{-11} μc/cc as a temporary permissible level with the recommendation that exposure levels be kept as low as operationally possible.[16]

B. SEVERITY OF HAZARDS:
1. *Health:* Low chemical toxicity for chronic or acute exposure.[1, 7, 16] Thorium compounds tend to remain at the site of deposition with the following exceptions: (a) when ingested excretion is almost complete (0.001% retained), and (b) when injected to the blood stream it tends to concentrate in liver, spleen, and bone marrow.[13] Injection of grams of thorotrast (thorium dioxide in liquid suspension) has produced cancer in experimental animals and in man.[4, 17] Radiation hazard to lung is high; probably comparable to uranium.

Fifty to seventy-five years of experience in refining thoria from monazite has produced no noticeable evidence of radiation injury or chemical toxicity. Industrial exposures averaged 10^{-10} μc/cc during this period.[1]

Ore processing results in emission of thoron, a gaseous daughter, which can offer an equally serious hazard as the thorium parent.

2. *Fire and Explosion:* Severe as finely divided metal. Powdered thorium metal is pyrophoric and may explode. Thorium metal powder as a dust layer or when dispersed as a cloud ignites spontaneously at 270–280°C. Lower explosive limit of dust in air 75 gm/m^3 or 75 mg/liter. Thorium hydride exhibits autoignition in air at 20°C. CO_2 blanket is not effective in extinguishing combustion.[8, 9, 10, 18]

II. Significant Properties

Occurs naturally in monazite or thorite. Chemical separation produces a mixture of thorium^{232} and thorium^{228} in radioactive equilibrium, and may drive off the active daughters creating an airborne hazard. Thorium decays slowly to form thoron gas which then decays to form stable lead^{208} with the emission of alpha and beta activity. Metal burns in air to form thoria (ThO_2).

Elementary Thorium:

Chemical symbol:	Th
Atomic weight:	232.15
Specific gravity:	11.2
Atomic number:	90
Half life of Th^{232}:	1.4×10^{10} years
Half life of Th^{228}:	1.9 years
Melting point:	1850°C
Alpha Energy:	4.0–4.2 mev (Th^{232})
Solubility:	Soluble in HCl, H_2SO_4, aqua regia. Slightly soluble in HNO_3.
Specific activity:	5.0 tons/curie
Surface dose rate:	40–100 mrep/hr (β) depending on age 50 mr/hr (γ)

Thorium Decay Series:

Series No.	Radio-element	Symbol	Historical name	Radiation emitted	Half-life
1	Thorium	Th^{232}	Thorium	alpha	1.4×10^{10} y
2	Radium	Ra^{228}	Mesothorium I	beta	6.7 y
3	Actinium	Ac^{228}	Mesothorium II	beta	6.1 h
4	Thorium	Th^{228}	Radiothorium	alpha	1.9 y
5	Radium	Ra^{224}	Thorium X	alpha	3.6 d
6	Radon	Rn^{220}	Thoron	alpha	54. s
7	Polonium	Po^{216}	Thorium A	alpha	0.16 s
8	Lead	Pb^{212}	Thorium B	beta	10.6 h
9	Bismuth	Bi^{212}	Thorium C	⅔ beta ⅓ alpha	60. m
10	Polonium	Po^{212}	Thorium C′	alpha	3×10^{-7} s
11	Thallium	Tl^{208}	Thorium C″	beta	3.1 m
12	Lead	Pb^{208}	Thorium D	none	stable

III. Industrial Hygiene Practice

A. Recognition: Principal use for metallic thorium as fertile material for nuclear breeder reactor cores and as an alloying material with some of the lighter metals. Thoria is used in small alloy percent in nonconsumable welding electrodes,[3] in gas mantles,[1] and in ceramics.

B. Evaluation of exposures: Inhalation exposure evaluation by sample collection of air dust and subsequent chemical analysis which consists of ion exchange separation, precipitation of Th as oxalate followed by colorimetric determination.[13, 18] When thorium is the sole long-lived radioactive contaminant, alpha counting may be used. Inasmuch as the total alpha activity varies with time, the approximate date of separation must be known before an accurate conversion of measured gross alpha activity can be made to gravimetric equivalents.[5] The x-ray fluorescent spectrograph has been used for analysis of thorium, but no data have been published. Urine analysis has been used as an indication of exposure.[13, 19]

C. Recommended control procedures: Local exhaust ventilation utilizing dust collectors is usually necessary. Powdered metal should be handled in inert atmosphere of argon or helium—CO_2 is not adequate as an inert atmosphere[8] and dust collection equipment should be nonflammable. Respirators should be worn in approaching burning metal.

Gloves provide adequate shielding from beta radiation dosage to skin for 40-hour work week. General ventilation prevents the accumulation of excessive quantities of thoron gas. Distance, shielding or exposure limitation may be required when extended sources exist.

IV. Specific Procedures

Careful introduction of burning thorium metal into copious quantities of water will suppress combustion. On fires which cannot be handled by immersion, liberal use of powdered graphite or other metal fire extinguisher may be effective. Small quantities of water sprayed on a fire are not effective. Powdered thorium metal should be transported as a sludge. Thorium scrap should be burned to the oxide under carefully controlled conditions.[8]

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Teflon TFE-Fluorocarbon Resins and Their Decomposition Products*

I. Hygienic Standards

A. Recommended maximum atmospheric concentration (8 hours):

1. *Dust:* None established. A value of 15 mg/m³ (on a nuisance basis) should be satisfactory.
2. *Decomposition products:* There are several types of Teflon TFE-fluorocarbon resins in commercial use, each differing in thermal stability and therefore differing in the amounts of the several decomposition products evolved at various temperatures. The critical aspects of the use of these at high temperatures are believed to be the temperature, the mass, and the surface area. Although much is known about toxicity of several individual decomposition products such as tetrafluoroethylene, hexafluoropropylene, octafluoroisobutylene, and hydrogen fluoride, no practical way has yet been devised to express a safe concentration of mixtures of these products. This is particularly true when polymer fume

* The use of fluorocarbon resins involves several commercial products. This Guide primarily pertains to Teflon and the information in it does not necessarily apply to other fluorocarbon resins.

Dr. Jonathan W. Williams (E. I. Du Pont de Nemours and Co.) assisted the Committee in the development of this Guide.

fever is the concern. The most practical approach is to judge the hazard by the maximum temperature used and to adjust ventilation and protective equipment accordingly.

B. SEVERITY OF HAZARDS:

1. *Health:* Oral toxicity is nil.[6] The resins are non-irritating and non-sensitizing to the skin. Inhalation hazard of dust at room temperature and containing no decomposition products is nil.

There is no hazard from pyrolysis products of the Teflon fluorocarbon resins at use temperatures of 200°C and below. Current studies may indicate this "safe" temperature to be 250–275°C. Among the products found when pyrolysis is carried out in glass equipment at 300–360°C are monomeric tetrafluoroethylene, hydrogen fluoride, silicon tetrafluoride (from the glass equipment), and an incompletely characterized waxy sublimate.[6] At 380°C and above, small amounts of the toxic gases, hexafluoropropylene and octafluoroisobutylene, have been isolated. Animal experiments show that octafluoroisobutylene is capable of producing irreversible lung injury.

Even at high use temperatures, the weight loss of Teflon fluorocarbon resins by pyrolysis is very small.[1]

The only known difficulties with humans using Teflon resins have consisted of temporary polymer fume fever ("the shakes") occurring with exposure to the polymer at processing temperatures of 340–385°C. This syndrome[2, 4] is similar to metal fume fever. It resembles an attack of influenza but recovery is rapid, usually occurring within 48 hours or less. The causative agent is unknown. It is believed that most occurrences during cutting or grinding fabricated parts of Teflon with high-speed tools have been associated with smoking Teflon-contaminated cigarettes.

2. *Fire:* Slight—Teflon resins are nonflammable below 690°C. At 690°C and above, decomposition products are flammable.

C. SHORT EXPOSURE TOLERANCE: Deaths were produced in laboratory rats after six hours exposure to the pyrolysis products of Teflon-6 at 300°C.[1, 2] With Teflon-1 a pyrolysis temperature of 350°C was necessary to produce fatalities. Most organic compounds produce lethal pyrolysis products to laboratory animals at temperatures below these.

D. ATMOSPHERIC CONCENTRATION IMMEDIATELY HAZARDOUS TO LIFE: Unknown.

II. Significant Properties

The Teflon fluorocarbon polymers are tough resins, usually white in color, and having a waxy-feeling surface.

Chemical formula:	$(—CF_2CF_2—)_x$ Teflon-1 and Teflon-6 are polymers of tetrafluoroethylene.
Molecular weight:	Very high. May be several million in certain types of Teflon.
Specific gravity:	2.15–2.28
Melting point:	327°C. Rubbery-like above 327°C
Solubility:	None.

III. Industrial Hygiene Practice

A. RECOGNITION: No identifying characteristics of taste, odor or irritation. Resins are used as electrical insulation materials, hose and pipe linings, gasket and packing materials, and in seals, bearings and piston rings.

B. EVALUATION OF EXPOSURES: To detect the presence of decomposition products of Teflon, the atmosphere may be monitored for fluorine-containing gases. Infrared spectroscopic methods may be used. Infrared scans for several of the fluorine-containing gases found in decomposition products of Teflon are included in the published literature.[1, 3]

C. RECOMMENDED CONTROL PROCEDURES: Processing, fabrication, and grinding equipment at high temperatures, and operations employing cutting or welding torches, soldering, or other sources of intense heat should be supplied with process ventilation. In machining operations the use of coolants is an effective method of preventing overheating.

Cigarettes or other tobacco products carried in the pocket in work area should be covered in order to prevent contamination with Teflon dust or particles.

In fighting fires involving a Teflon resin, masks should be worn that provide protection against acid fumes, organic vapors and finely-divided particulate matter.

IV. Specific Procedures

A. First aid: Remove immediately from exposure. Place individual at complete bed rest. Call a physician.

V. References

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Because of space limitations, it is impossible to list all methods of exposure evaluation. The selections have been made on the basis of current usage, reliability, and applicability to the usual industrial type of exposure. Any specific evaluation and/or control problem will involve professional judgment. This can best be done by professional industrial hygiene personnel.

Respiratory protective devices are commercially available. Their use, however, should be confined to emergency or intermittent exposures and not relied upon as primary means of hazard control.

A relative scale is used for rating the severity of hazards: nil, low, moderate, high, and extra hazardous.

Hygienic Guides Committee

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News of Local Sections

North Texas Station

This section now has 21 members and holds four bimonthly meetings each year. In May a one-day Occupational Health Conference is held jointly with the Gulf Coast Section and the University of Texas. The next meeting date is November 30, 1059.

Plans are being considered for joint sponsorship by the Section with the U.S. Bureau of Mines of an exhibit to the Health Fair, November 28–December 6, 1959. The Fair will be held in the main arena of the Municipal Auditorium in connection with the Dallas County Medical Society during the forthcoming meeting of the American Medical Association.

Western New York Section

More than 50 Section members and guests attended the June 8th dinner meeting in Rochester's Sheraton Hotel. Dr. Charles R. Williams, a past president of AIHA and Assistant Vice-President of Liberty Mutual Insurance Company in charge of Industrial Hygiene Services, delivered a very knowledgeable, behind-the-scenes, uninhibited talk on "Radiation Control." He left us with a better understanding of the maneuvers of the state and federal governments, the Public Health Service, and the Atomic Energy Commission with regards to the control of radiation sources.

Section President Herbert I. Miller, Jr., recently underwent surgery but is now back on his feet and the job, having recovered nicely.

Philadelphia Section

New officers of this Section are: Jake Sharrah, President; Emmert M. Baxter, President-Elect; Jesse Lieberman, Secretary; A. A. Maier, Treasurer; Richard C. Charsha and Dr. Joseph F. Treon, Jr., Directors. These officers were elected at the March meeting which featured a field trip to the Research and Development Center of the Armstrong Cork Corporation at Lancaster, Pennsylvania. Dr. Thomas Mariner gave a talk and demonstration on "Noise Suppression."

The Section participated in a joint meeting with ASSE, INA, and IMA at Bayuk Cigar Company in May. Over 100 persons attended. A panel discussed the role of each organization in industrial health. Members of the panel were: William A. Shoemaker, AIHA; Mrs. Maude W. Wandell, INA; Dr. Gilbert B. Meyers, IMA; and William E. Helms, ASSE.

The September meeting was held at the Engineers Club, Philadelphia, and Adrian L. Linch of DuPont Company spoke on "Chemical Cyanosis—Cause, Effect, and Prevention." The next meeting will be November 10, 1959, with a field trip to the Philadelphia Naval Base.

Northwestern Michigan Section

The Section had their first meeting of the new fall and winter program on August 24, 1959, at the Dow Chemical Company Library Auditorium in Midland. Dr. E. C. Vigliani of the University of Milan, Milan, Italy, spoke on "Considerations in Lead Poisoning."

New England Section

At the September meeting at the Publick House, Sturbridge, Massachusetts, the speaker was Mr. Elmer P. Wheeler, President of the AIHA and Assistant Director, Medical Department, Monsanto Chemical Company, St. Louis, Missouri. Results of a mail ballot of Section members approving changes in the by-laws of the Section were announced.

Future dinner meetings are planned for November 19, 1959, January 21, and March 11, 1960. An all-day meeting has been proposed for May 20, 1960.

Personnel Notes

Dr. Henry F. Vaughn, first dean of the Michigan University School of Public Health has retired. He had been Dean of the School of Public Health since it was established in 1941. Following retirement, he plans to remain active in public health work and will devote his time to the National Sanitation Foundation at Ann Arbor, of which he is president, and to trustee duties with W. K. Kellogg Foundation of Battle Creek.